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STUDIES CONCERNING

GLYCOSURIA AND DIABETES

BY

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TO MY PARENTS

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PREFACE

The present work represents three years of research in the laboratory of Preventive Medicine and Hygiene of the Harvard Medical School. My appreciation is here expressed to Prof. M. J. Rosenau for the hospitality and privileges accorded to me in the laboratory, and for the bestowal of the Charles Follen Folsom Fellowship with its income of $525 per year; furthermore, to him for recommending, and to the Trustees of the Proctor Fund for granting, a gift of $300. The above sums have partially defrayed the expenses of the research, which for the most part has been personally supported. Also, toward the expense of publication, a gift of $100 has been received from Mr. T. Jefferson Coolidge of Boston, and a loan of $1600 from the Department of Preventive Medicine and Hygiene.

Hearty thanks are due to Prof. A. I. Kendall, formerly of this Department, now of the Northwestern University Medical School, for reading the manuscript of Chapters IV and V, for valuable information touching their subject-matter, and for numerous personal favors. The extent of my obligation to Dr. H. L. Amoss is also acknowledged with pleasure, for his indispensable assistance in a multitude of operative and other procedures, and for personal favors at all times. Outside of this Department, an unusual debt of gratitude is due to Prof. F. B. Mallory, for voluntarily assuming the burden of working up the pathological material, and for guidance and instruction in the study of it. This kindness has made possible the writing of Chapter XXI, of which Dr. Mallory also has read the manuscript. For good offices in connection with publication I am indebted to Dr. Elliott P. Joslin, Dr. Joseph H. Pratt, and Prof. Harvey Cushing, and to the last-named two for valued personal communications. The microphotographs are the work of Mr. L. S. Brown of the Massachusetts General Hospital, whose interest and care have been highly appreciated.

So far as I am aware, there is no recent work in the English language covering the difficult field of glycosuria and diabetes.

In other languages, these subjects are treated admirably in the books of Naunyn, von Noorden, and Lépine on diabetes, of Pflüger on glycogen, of Biedl on internal secretion, and of Rosenberger on glycosuria. The scope of the present monograph is identical with none of those. It aims primarily to present the results of research. Its spirit is that of an enlarged journal article. A few representative animal protocols are contained in the appendix. The manuscript was transmitted for publication November 1, 1912, and as far as practicable includes the literature up to that date. No compilation of a complete bibliography has been attempted; the references given are those actually used in connection with the research, and whenever an author's name is mentioned in the text, the corresponding reference will be found in its alphabetical order in the back of the book. The subject of diabetes heretofore has been what William James might have called " a big, blooming, buzzing confusion." It is hoped that the present investigation may tend to simplicity and order. The detailed review of certain portions of the literature is for the purpose of orienting my results with those of others, and for the convenience of prospective investigators, or of physicians who may be interested in the clinical suggestions.

The purpose from the outset was an improved therapy of diabetes. To this end, it was necessary to seek information concerning the physiology of sugar and the origin and nature of diabetes, to produce a satisfactory reproduction of human diabetes in laboratory animals, and to try various methods for modifying the disease thus produced. It is believed that the cure of diabetes is now a feasible experimental problem.

FREDERICK M. ALLEN.

POMONA, CALIFORNIA.

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CHAPTER I.

GLYCEMIA, GLYCOSURIA, AND GLUCOSE-TOLERANCE.

1. Carbohydrates of Normal Blood.

In harmony with our vast ignorance concerning the blood in other respects is the existing uncertainty concerning one of its simplest components, viz: the carbohydrates. From a superficial standpoint, nothing should be easier to study than the various properties and constituents of the blood. In actual practice, and as respects fundamentals, few studies have proved more difficult or more deceptive.

It may be taken as fairly well settled that the principal sugar of the blood is d-glucose, the percentage of which in normal human beings ranges from 0.06 to 0.105 per cent. According to von Noorden, the average may be set at 0.085 per cent. Concerning the lower limit there has been little debate; the lowest normal figures seem to be 0.06 per cent by Lyttgens and Sandgren and 0.061 by Tachau; Liefmann and Stern placed it at 0.065 per cent, and Lepine and Frank at 0.07 per cent. The upper limits have been most in dispute, because of the question as to what constitutes hyperglycemia. This limit has been set by various authors as follows: 0.105 per cent (Liefmann and Stern, Hollinger, Weiland); 0.095 (Lepine); 0.09 (Frank, Neubauer, Stilling, Forschbach and Severin); 0.084 (Tachau); 0.11 per cent [in serum, Schirokauer (3)]. Hegler's results constitute an exception, for he finds, by the Bang method, fasting values of 0.0734 per cent minimum to 0.16 per cent maximum.

There is a generally recognized clinical need of a method for quantitative blood-sugar determination which shall be quick, accurate, and adapted for use with small blood-samples. Moeckel and Frank introduced a method requiring only 5–10 cc. blood and 35–40 minutes time. Also, in the attempt to meet this need, various colorimetric methods have been proposed. These tests,

e.g., those of Reicher and Stein, Wacker, Herzfeld, etc., consist in reactions with furfurol, methylene blue, safranin, etc. The general criticism of them is that they react to all the reducing substances of the blood (including glycuronic acid), hence give too high values. Reicher and Stein, for example, find normal limits of 0.09–0.15 per cent, and Wacker finds 0.14–0.18 per cent. These figures include more than what is ordinarily meant by "blood-sugar," yet do not include the whole of what Lepine and Pavy call the "total" sugar (*i.e.* "immediate" + "virtual" sugar; see below). One interesting point that seems to be brought out by these methods is that in conditions in which the glucose of the blood is known to be increased, the other reducing substances are also increased, as if there were a balance between the different components. This might correspond to Pavy's observation that intravenously injected glucose is partly changed into other forms. Of an entirely different nature are the colorimetric methods of Autenrieth and Tesdorpf, and Forschbach and Severin. The principle here is the partial reduction of a Bang solution by the sugar contained in a small sample of blood, the degree of decolorization being then determined by a delicate colorimeter. Forschbach and Severin claim that their method is feasible with blood-samples of less than 2 cc., and is accurate to within 1 per cent of the quantity of sugar present.

The evidence for the existence of carbohydrates other than d-glucose in the blood may be classified as follows: (1) differences between reduction and polariscopic tests; (2) fermentation tests; (3) changes produced by merely allowing blood to stand; (4) increase of reduction as result of treatment with ferments or with acids; (5) perfusion experiments; (6) attempts at isolation and identification of certain members of the group. Obviously, the subject is almost hopelessly complex. The possible substances to be considered include sugars, glycogen, dextrins or dextrin-like bodies, jecorins, glucosides, glycoproteids or other firm or loose protein-sugar combinations, and glycuronic acid and compounds comparable to it. And even with the sixth and most difficult method, the question inevitably arises whether the substance finally isolated actually existed in the blood as such, or whether it was formed or split off in the process of analysis. It is not fully determined to what extent the substances when present occur as cell-constituents, to what extent their presence is accidental or occasional, and to what extent they may represent, as does glucose,

a food-material in transport from the organs of supply to the organs of consumption. Lepine habitually considers the blood-sugar in two divisions, "immediate" and "virtual." The former is the reducing portion, which can be estimated by titration with copper; the latter includes all the other actual or potential carbohydrates of the blood, and is measured by the increase of reduction which results from boiling the blood with an acid, especially hydrofluoric. The two portions are approximately equal; when the "immediate" sugar is about 0.1 per cent, the "total" sugar is about 0.2 per cent. The views and methods of Pavy are similar. Discussion and methods are given in the books of Pavy and Lepine, also by Lepine and Boulud (1 and 6). Lepine and Boulud (10) present comparisons of the two moieties under varying conditions (arterial and venous blood, asphyxia, hyperthermia, infection, etc. Phloridzin increases the "virtual" sugar of venous blood). Bierry and Fandard have lately published a method, and analyses in different species, making the interesting claim that the "total" blood-sugar is a constant; species, such as birds, rich in "free" sugar, have correspondingly little "virtual" sugar, and *vice versa*. [But according to Loewit's figures, the "immediate" sugar of the frog exceeds the "total" sugar of human blood.] Except by the above authors and their pupils, the "virtual" moiety of the blood-carbohydrate is ignored in routine blood-examinations; and as yet no definite physiological or diagnostic importance has been demonstrated for this moiety.

The above-mentioned substances in addition to glucose may be considered in order. The sugars are levulose, iso-maltose [the distinction from maltose may be difficult or doubtful; see Pflüger (1), pp. 432–33], and pentoses; Rosenberger (p. 316), refers to authors who have found mannose, and to Lepine as having found saccharose [portal blood?]. Mention must also be made of a hypothetical "rest-sugar," said to be reducing but not fermentable. Erlandsen (1) reckons that one-fourth of the rabbit's blood-sugar is not dextrose but "rest-sugar." Lyttkens and Sandgren have studied the "rest-sugar" in the blood of man and the domestic mammals, finding it in the corpuscles. On the other hand, Forschbach and Severin, and others, find no such substance, and its existence must be considered doubtful. Hammarsten (p. 257) considers the presence of any sugars other than dextrose and levulose as undecided.

Glycogen is present in normal blood in traces (about 0.0025 per cent). It is a constituent of the leukocytes; it probably does not occur dissolved in the plasma, except as accidental traces from broken-down leukocytes, and the general opinion is that the blood does not carry it as a pre-formed foodstuff to the tissues, but that the muscle and other cells form their own glycogen. In diabetes the glycogen content of the leukocytes may be found increased, and glycogen may also occur free in the plasma.

Dextrins or similar substances have been found in the portal blood during carbohydrate digestion. In early analyses by Magendie and Frerichs [ref. by Pflüger (1), p. 434] dextrin was isolated from the peripheral blood. The exactness of these analyses may be open to question now; but the normal urine contains substances of dextrin nature, and it is merely a choice whether these substances are formed in the kidney or transported to it by the blood.

Jecorins, the well-known compounds of lecithin and sugar first discovered by Drechsel, have not fulfilled the high hopes once entertained for them. They have not solved the problem of diabetes, nor of the permeability of the kidney for sugar; nor has any diagnostic or other practical value been found for them. Their very existence is still under debate, both as a question of their occurrence in living blood or tissue, and the broader question whether any such compounds exist at all, or whether they are mere mixtures. It suffices here to state that these alleged compounds have been investigated especially in the liver and in the blood; that the kinds and the quantities of jecorins from these different sources are different, and there are also wide differences between different species of animals; that some jecorins are reducing substances and others are non-reducing; that at any rate the greater part of the blood-sugar is not in the form of jecorin; and that from the strictly physiological standpoint jecorin has proved less useful as a compound than as a basis of analogy; thus the advocates of combined blood-sugar habitually speak not of jecorins, but of "jecorin-like substances."

The presence of substances of glucoside nature is suggested by Lepine, because the reducing power of the blood is increased at the expense of the "virtual" sugar by the action of emulsin or especially invertin.

Part of the sugar classified as "virtual" is supposed to be in the form of albumin compounds, according to Lepine and Boulud (9).

It is also a favorite idea of Pavy that sugar is transported as a side-chain of an albumin molecule.

Glycuronic acid is in traces a constituent of normal blood, and may be found increased in diabetes, in asphyxia, and after very large doses of sugar. Various writers have regarded it with probability as a product of imperfect combustion of glucose. For a discussion one may refer to Naunyn (p. 12) or to Magnus-Levy [(4), p. 159], or von Noorden [(3), Vol. 3, p. 577]. Hammarsten (p. 257) mentions the presence of two glycuronic acids, as found by Lepine and Boulud.

Very little is known concerning the possible relations and mutual transformations of the different carbohydrates in the blood. Probably all of them, even the so-called "free" sugar, exist normally in combination with colloids rather than as isolated crystalloid substances; the view is intrinsically probable, and the evidence will be discussed in Chapter VI. Certain organs may apparently produce transformations of the blood-carbohydrate. Levene, Biedl and Kolisch, Pavy Brodie and Siau, and Lepine (5) have found in phloridzin poisoning more sugar in the urine and the renal-vein blood than could be accounted for by the sugar-content of the blood of the renal artery; some of the earlier methods are questionable, but all the claims cannot be summarily dismissed. Embden perfused the normal glycogen-free liver with normal blood, and obtained well-marked increase of sugar; when the maximum was attained, the same blood perfused through a fresh liver showed further increase of sugar, or the same liver perfused with fresh blood again increased the sugar; a sugar-forming substance was concluded to be present in both blood and liver. The blood of different vascular areas is claimed to show different sugar-values; *e.g.*, the carotid blood has been found by Lepine to contain more than the blood of the right heart. Also, according to Lepine, a partial transformation of "virtual" into "immediate" sugar occurs in the lungs. On account of the well-founded opinion that the muscles use sugar, it is commonly accepted that the venous blood contains less sugar than the arterial blood. Both Pavy and Lepine declare that the venous blood may contain equal or even higher glucose percentages as compared with the arterial. In view of the possible unknown relations between the different reducing and non-reducing blood-carbohydrates, their statements, based on numerous analyses, cannot be entirely disregarded. Lepine and Barral attempted to prove the

diminished utilization of sugar in diabetes by comparisons between the arterial and venous blood-sugar; but their claims were disputed by Chauveau and Kaufmann. All these numerous questions are made very uncertain by the analytical difficulties in dealing with such small percentages of sugar in an albuminous medium, and still more by the wide fluctuations to which the blood-sugar is subject in consequence of different operative manipulations.

The important question of the distribution of the blood-sugar between plasma and corpuscles is also under debate. One point seems admitted by nearly everybody; that is, that the erythrocytes contain some sort of reducing substance. But with the question whether this reducing substance is glucose, the dividing line between two hostile camps is reached; and, in the larger camp, agreement as respects details is absent. Bang in particular holds out against the occurrence of glucose in the corpuscles. In his paper (2), he briefly sums up a polemic by grouping Michaelis and Rona, Hollinger, Lepine, Frank and Moeckel and Bretschneider as upholding the view that the blood-sugar is divided between plasma and corpuscles; and himself and his pupils as maintaining that glucose exists only in the plasma. He admits that the corpuscles contain reducing substance; but he himself has failed in the effort to produce a glucosazone; if the substance is glucose the osazone should be easy to prepare; and he challenges his opponents to produce it. Edie and Spence, on the basis of dialysis experiments, claim that the corpuscles are devoid of sugar. Rona and Takahashi claimed to identify glucose in the corpuscles by reduction, polarization and fermentation tests. Michaelis and Rona found varying relations under varying experimental conditions (adrenalin, etc.), sometimes even the absence of sugar from the corpuscles while it was present in the plasma. Brasol, with intravenous sugar injections, found that the sugar-content of the plasma rises more rapidly than that of the corpuscles, but the corpuscles retain the sugar somewhat more tenaciously than the plasma. Authors [see Rona and Takahashi] have found a different distribution of the sugar in different animal species as well as in different forms of glycosuria. Lyttgens and Sandgren have investigated the blood of man and domestic mammals, and found uniformly that the corpuscles contain no glucose, but only "rest-sugar" (*i.e.*, reducing but non-fermenting). Forschbach and Severin have found that the corpuscle-sugar is glucose, and fer-

ments completely. There is a practical question whether sugar determinations should be made with the whole blood or with the plasma. Von Noorden [(1), p. 8], on the basis of the researches from his clinic, maintains the equal distribution of sugar between corpuscles and plasma. Hollinger found differences between blood-sugar and plasma-sugar. Frank accepts 0.12 per cent as the normal upper limit for plasma-sugar, as against 0.09 per cent for the whole blood. Forschbach and Severin have also found the corpuscles to contain less sugar than the plasma. Lepine and Boulud (5) presented a method by which they found marked differences between corpuscles and plasma; but in a case of diabetes with blood-sugar of 0.35 per cent, the same authors (8) found the distribution equal between plasma and corpuscles.

In summary, it may be said that the greater weight of opinion is that glucose exists in both corpuscles and plasma, but that its distribution between the two is either regularly or frequently unequal. It is still the commonest practice to use the whole blood for sugar determinations, but according to the best and latest work, the use of serum is somewhat preferable and is likely to win general adoption. The most recent experiments and review are by Schirokauer (5); he finds that though the blood-sugar varies as above mentioned, the serum-sugar in health and in various diseases remains fairly constant at about 0.11 per cent; the chief variations are therefore in the corpuscle-content. One of the interesting fields of research in this subject would seem to be whether the distribution of the blood-sugar between corpuscles and plasma is altered in diabetes, in correspondence with hypothetical alterations in the state of combination of the sugar.

2. Glycolysis.

Claude Bernard was familiar with the fact that the sugar gradually disappears from blood on standing. Lepine was the first to perform the tests with aseptic methods, and his proposed explanation of diabetes on the basis of a glycolytic enzyme supplied to the blood by the pancreas possesses historic interest. The literature is massive, and a review would be superfluous; the fullest treatment of the subject is found in the text of Lepine. Doyen and Morel refer to Arthus, and support his view that the plasma contains no glycolytic ferment. Lepine and De Meyer

admit that it is contained only in the leukocytes; addition of distilled water increases the glycolytic power of blood by destroying the corpuscles. Because of the exceedingly feeble power of the blood to destroy glucose, and because of the failure to establish any constant differences between diabetic and non-diabetic blood, Lepine no longer considers this ferment to give an adequate explanation of diabetes, and its importance is insisted upon most strongly by De Meyer. The changes occurring in the sugar when blood stands *in vitro* are complex. Lepine recognizes a disappearance of sugar due to glycolysis, and a new-formation of "immediate" from "virtual" sugar; a distinction is thus drawn between the "real" and the "apparent" glycolysis. Lepine and Boulud (11) have devoted a paper to comparisons between these phenomena under various experimental conditions (pancreatectomy, etc.). Vandeput found that the glycolysis is more rapid with higher percentages of sugar.

Even the most recent work on the subject contains radical contradictions not only of opinion but also of fact. Edelmann finds the intensity of glycolysis greatest within the first six hours; the power is retained in laked blood, but greatly diminished in depancreatized dogs, and some time after operation may be entirely absent. After thyreo-parathyroidectomy the process is delayed for the first six hours, thereafter is as in normal blood. Abderhalden and Rathsmann [ref. by Milne and Peters] find that normal dog-serum possesses no glycolytic power, but acquires this power after a large meal or the ingestion of large quantities of sugar. Milne and Peters find no glycolytic action under the above conditions. Contrary to French authors, they find no evidence of any glycolytic enzyme; laking the blood with distilled water prevents the destruction of glucose. The sugar that disappears when blood stands is taken up and destroyed or changed by the corpuscles; it cannot be recovered as glucose. The process is active for twenty-four and forty-eight hours. The serum and corpuscles of depancreatized diabetic dogs or those with phloridzin glycosuria behave in all respects like the normal; the corpuscles destroy sugar as actively as normal.

In general, it may be concluded that the loss of sugar by blood *in vitro* presents interesting unsolved problems, especially for the chemist. Its interest from the standpoint of diabetes is purely historical. It is an exceedingly feeble process [*e.g.*, of the tiny quantity of blood-sugar, Milne and Peters found one-third to be

destroyed in twenty-four hours]. As in the case of other post-mortem phenomena, differences between the diabetic and the normal fail to be demonstrated. Its value in the study of diabetes has been purely negative.

3. Influences Affecting the Normal Blood-Sugar.

Reduction of blood-sugar below the normal lower limits is a difficult and unusual matter in the normal organism. Approximately the normal percentage is stubbornly maintained through prolonged starvation, almost up to death. Phloridzin poisoning, adrenal insufficiency, or other conditions reported associated with reduced blood-sugar, are all distinctly pathological. The only condition which should perhaps not be classified as pathological, and in which low blood-sugar occurs, is simple exhaustion. For example, Weiland (1) found that exhausting muscular exercise reduces the percentage of blood-sugar.

Elevation of the percentage of blood-sugar is more frequently observed. The blood-sugar of infants is normally a trifle high. In women there may be slight hyperglycemia with menstruation. Hyperglycemia in pregnancy is not usual, according to the recent study by Schirokauer (3). Special influences described as increasing the blood-sugar are [besides ingestion of sugar; see Section 15], muscular labor, heat, cold, hemorrhage, traumatism, nervous or emotional disturbances, drugs, and infectious and other diseases. In the case of the first three, increased need of sugar is supposed to cause increased sugar-transport. It may be noted also that the first two are productive not only of increased transport of sugar but of increased ability to use it; they diminish or prevent alimentary glycosuria. That muscular labor under some conditions diminishes blood-sugar, as stated in the preceding paragraph, is an assured fact. That it may under other conditions increase the glycemia is not improbable, and is reported as a fact by Reach (4). He claims to have found the increase in the early stages of muscular work; but his conclusions cannot be definitely accepted unless confirmed, for the muscular movements in his animals were produced by strychnin or by galvanization, and either of these may itself be a cause of hyperglycemia. Likewise the struggling of tied animals [mentioned by Gigon (2)] proves nothing, because of the emotional element. Fisher and Wishart found values of 0.19 and 0.14 per cent in a dog during cocain convulsions; but cocain is itself a cause of hyperglycemia; and in convulsions from any

cause, there is no information whether some "call" from the muscles produces increased sugar-formation, or whether the nervous state responsible for the convulsions is responsible also for the sugar-formation. The effects of temperature vary somewhat with the cause of the temperature. Senator (2) finds that increased temperature, produced either by artificial heating or by brain-puncture, causes increase of the blood-sugar, but not sufficient to lead to glycosuria. He gives the literature of the subject. Lepine and Boulud (7) report that application of external heat, even though the body-temperature be raised to 41 degrees, affects the blood-sugar very little. But in infection, even if the hyperthermia is moderate, there is considerable disturbance of the blood-sugar, sometimes a marked hyperglycemia, sometimes a hypoglycemia. Lüthje demonstrated an increased excretion of sugar from cold in diabetic dogs (extirpation not quite complete). Embden, Lüthje and Liefmann showed that the blood-sugar of normal dogs is increased by cold. Extreme cold is known to be conducive to glycosuria. Whether moderate cold may ever increase the sugar-tolerance seems not to have been investigated. Hemorrhage produces hyperglycemia by virtue of some action exerted directly upon the liver without intervention of the nervous system; neither double splanchnicotomy nor double epinephrectomy can prevent it, according to Nishi (1). Many sorts of injuries or nervous disturbances, and many sorts of drugs, may be responsible for hyperglycemia, even to the point of glycosuria. Here we are departing from the normal, and the general subject must be considered in later chapters. Any of the agencies which in extreme degree may cause glycosuria, may in lesser degree cause a certain amount of hyperglycemia. Among drugs, anæsthetics, hypnotics and diuretics have well-known hyperglycemic tendencies. There may be room for inquiry whether all the patients in whom hyperglycemia has been reported in connection with nephritis or other conditions, have been kept suitably free from the possible disturbing effects of drugs.

There has been considerable disagreement concerning hyperglycemia in nephritis. Von Noorden [(3), p. 499] considered the blood-sugar to be normal, but his later opinion [(1), p. 110] is in favor of hyperglycemia. Lepine [(1), p. 194] states his experience that nephritic patients in the stage of cachexia show hypoglycemia, but when hypertension exists, hyperglycemia is frequently found. Neubauer (2) reported blood-sugar analyses in a series

of nephritic patients with high blood-pressure. The highest was 0.21 per cent, the lowest 0.0791 per cent; the average was well above 0.1 per cent; in other words, generally a well-marked hyperglycemia. None of the patients showed glycosuria. Even in cases of diabetes complicated with nephritis, the patients might be free from glycosuria for weeks, with blood-sugar constantly above normal. Weiland (2) found no increase of blood-sugar except in cases of uremia, apoplexy, and eclampsia. Frank (2) found no increase of blood-sugar in ten cases of increased blood-pressure with or without nephritis. Tachau (1*A*) found in chronic nephritis with increased pressure a slight increase of blood-sugar, mostly 0.102–0.106 per cent. Stilling obtained entirely negative results as respects hyperglycemia in nephritis. Increase of blood-sugar may be found in exophthalmic goitre and in nervous disorders, or any of the other conditions associated with clinical glycosuria [see Chapter XII]. Hegler has found hyperglycemia in all or many of the patients whom he has investigated in the following diseases; pneumonia (only 1 patient in 40 had normal blood-sugar), typhus, angina, erysipelas, variola, hepatic cirrhosis, anemia, CO-poisoning, and nephritis. He found normal blood-sugar percentages in catarrhal icterus, chronic alcoholism, and cases of increased blood-pressure without nephritis.

4. Blood-Sugar of Different Species.

Lyttgens and Sandgren present the following table of dextrose-percentages in the serum.

	Per cent
Man	0.063
Sheep	0.064
Pig	0.082
Beef	0.086
Horse	0.098
Rabbit	0.222
Guinea-pig	0.248
Cat	0.291

Wacker, by the colorimetric method which showed 0.14–0.18 per cent in human blood, found 0.281 per cent in the blood of a white mouse.

A general opinion among authors is that small animals with active metabolism and large heat-radiating surface have the highest blood-sugar. It is doubtful if we yet know the normal

blood-sugar of these species. In the mouse, for example, a blood-sample such as is necessary for sugar-determination represents a large hemorrhage. In other species, the investigator is between the Scylla of emotional hyperglycemia without anæsthesia, and the Charybdis of toxic and asphyxial hyperglycemia with anæsthesia. The above figures for the cat are very probably too high, for the animals were anæsthetized under a bell-jar, and thus subjected to emotion, ether, and asphyxia; control-tests of the urine might possibly show glycosuria in such cases. If a gentle cat could have the jugular exposed by a brief operation with freezing or weak cocain, then be returned to its cage for an hour or so, and if finally a specimen of blood might be taken from the vein with a needle with as little disturbance as possible, lower percentages might be expected. A quiet comfortable animal is a desideratum in all blood-sugar tests.

For the rabbit, the following reported values may be compared. [See also literature in the recent paper by Schirokauer (3)].

0.07–0.16 per cent, average 0.12 per cent (Schenck).
0.09 per cent (Lewandowski).
0.09–0.16 per cent, average 0.12–0.13 per cent (Andersson and Erlandsen).
} Ref. by Erlandsen (1).

0.15 per cent maximum; never up to 0.2 per cent (Rose).
0.075–0.165 per cent, average 0.109 (Nishi 1*A*).
0.222 per cent (Lyttgens and Sandgren).
0.21–0.27 per cent (Wacker; colorimetric method).
0.10–0.11 (in serum, Schirokauer).

The rabbit is an animal subject to emotional and traumatic hyperglycemia, and thus the above discrepancies are apparently explained. The most trustworthy figures are the lowest. Recent evidence, therefore, overthrows the view that the normal blood-sugar of the rabbit is exceptionally high; rather, it is very near the human percentage. It is not improbable that the blood-sugar of all or most mammals may be found to be a rather constant figure.

The blood-sugar of the dog may be considered identical with that of man; possibly the normal values may range a trifle higher. Donath and Schlesinger review the earlier analyses and find that the trustworthy ones did not exceed 0.13 per cent. They them-

selves found a series of percentages lying slightly below 0.1 per cent. Other reports are as follows:

0.065–0.105 per cent (Liefmann and Stern).
0.08–0.14 per cent (Lepine).
0.07–0.09 per cent (Reach (4)).
0.077 per cent (Michaud).
0.14–0.18 per cent (same as human; colorimetric method) (Wacker).
0.13 (Bierry and Fandard).
0.11 (Fisher and Wishart).

For birds, Kausch (1) gives the high figure of 0.12–0.18 as normal. Bierry and Fandard give 0.23 per cent for the chicken. Giaja has found 0.175–0.24 per cent as the normal limits for the chicken, varying somewhat with age. Others also have found high values.

All warm-blooded animals have glucose in their blood. Probably minute traces are present in all vertebrates; but cold-blooded animals present wide variations. The longest series of sugar-analyses in frog-blood is probably that of Loewit (3). In his earlier experiments he found that the method of obtaining the blood makes considerable difference; and the consequences of his methods at that time were blood-sugar values of 0.409–0.84 per cent. By a quicker procedure in obtaining the blood, he found the blood-sugar of normal frogs to vary from 0.24 to 0.37 per cent, average 0.305. In depancreatized frogs the average blood-sugar was 0.775.

Spallita investigated the blood of sea-turtles, and found in it dextrose and maltose. He refers to Pavy's finding of dextrin and maltose in the liver of mammals as intermediate stages between glycogen and glucose, and suggests that the very large proportion of maltose found in the turtle-blood may be due to the slowness of physiological processes in this animal, the maltose diffusing out into the blood-stream before it can be fully converted into dextrose. But at least in his French publication, Spallita does not make clear whether the entire difference in reduction before and after boiling with acid can be accounted for on the basis of maltose, or whether there may be other unknown forms of "virtual" sugar present. Nishi (2) found that normal land-tortoises (Testudo europæa) have no blood-sugar. Such a difference between closely related animals is interesting. Diamare (2) determined

that the blood of Scyllium and of Torpedo (and probably other selachians) normally contains no glucose. But he suggests the possibility that glucose may be present, but that some other substance present interferes with its detection, except when the normal traces are exceeded. That all these animals are capable of glycemia is shown by the high percentages of glucose that appear in their blood after extirpation of the pancreas. It would be interesting to know if their blood feeds their muscles with carbohydrate in some other form than glucose.

Bierry and Fandard (2), who assert that the "total" blood-sugar of all species is a constant, have further proposed the law that the "immediate" sugar and the body-temperature are parallel, the sugar-supply, combustion, and temperature being related phenomena. They support this generalization by references to the blood-sugar of several species. The marmot awake has a blood-sugar of 0.117 per cent; dormant, its blood-sugar is 0.009 per cent. Portier is said to have found blood-sugar in selachians to the extent of a few decigrams per thousand. Bierry and Giaja are quoted, fixing the arterial blood-sugar of the octopus at 0.03 per cent. This view is an interesting addition to the common opinion that small animals with active metabolism have the highest blood-sugar. But neither idea is absolutely valid. Thus, the dog has a considerably higher temperature than man, yet the best analyses place its blood-sugar little, if any, above the human. The most notable exception is the frog, with a normal blood-sugar higher even than that of birds. There is no general law governing the blood-sugar of different species.

5. Carbohydrates of Normal Human Urine.

The reducing substances of normal urine are commonly said to be glucose, iso-maltose, uric acid, creatinin, and compounds of glycuronic acid; and the carbohydrates are said to be glucose, iso-maltose and dextrin (or "dextrin-like substances"). Some of the literature of the subject is given by Hammarsten (p. 711). In addition, there is the long paper by Moritz covering the whole of the copper-reducing constituents, proving that glucose is present, and discussing physiological alimentary glycosuria. Pavy and Siau (1) found that the sugar of normal blood, muscle, and urine is glucose and iso-maltose. Breul, in Naunyn's clinic, concluded from his analyses that the sugar-excretion of normal human beings on ordinary diet varies between 0.36 and 1.95 g. per day,

or a percentage between 0.027 and 0.178 per cent, generally 0.05 to 0.06 per cent. Heavy carbohydrate feeding prolonged for eight days was found not appreciably to increase the output. When after a 24-hour fast a heavy starch-meal was given, the excretion rose only to 0.203 per cent. The largest meal of rice that a Japanese investigator, Miura, could eat, had negative results. Schöndorff (1) reinvestigated the whole question, and concluded that every normal human urine contains sugar in measurable quantity, ordinarily between 0.0105 and 0.0274 per cent; but excessive carbohydrate intake may raise this to 0.1 per cent. He reserved the question whether suitable diet can cause complete disappearance of sugar. This point has been touched by Barantschik, who reports that complete withdrawal of carbohydrate for five days has practically no effect on the normal trace of sugar in the urine.

The dextrin or related substances present in urine belong in the achroödextrin group. Alfthan (1 and 2) found that the average quantity of dextrin in a normal 24-hour specimen of human urine is 0.15 g. He, also Rosin and Laband at an earlier date, also von Noorden and others, have discovered immense increase of the dextrin excretion in some cases of diabetes; and the amount of dextrin is found to increase with increasing severity of the disease. Alfthan's figures for the 24-hour excretion in diabetes range from 0.8 g. to 24.4 g. of pure, ash-free dextrin. Von Noorden [(1), p. 114] mentions one of his cases in which during twelve days, as the patient rapidly went downhill to death in coma, the dextrin excretion increased from 3–4 g. daily to 17–27 g. daily.

A work which may change existing views is the recent paper of Oppler. He has criticized the existing methods for the determination of small traces of dextrose in blood or urine, and the accuracy of the colorimetric methods [see Hasselbach and Lindhard, Wender, and the previous blood-sugar references]. With a more accurate procedure, he finds that normal human urine contains reducing, fermentable, optically inactive substances corresponding to about 0.04 per cent dextrose; but the possible content of true dextrose is below 0.01 per cent, and in one case below 0.001 per cent. The supposedly well-established existence of a physiological glycosuria is called in question by his work. The absence of dextrose from normal urine, if confirmed, should be a fact of some theoretical interest in connection with diabetes and the combined state of the bood-sugar.

6. Carbohydrates of Urine of Normal Animals.

Burguburu (ref. by Rosenberger, p. 331) found guinea-pigs inclined to show slight glycosuria. Zanda (*2*) finds the same with rabbits. Lombroso (16) refers to Pavy's observation that a glycosuria of 0.2–0.3 per cent is normal in herbivorous animals. In my comparatively short series, I have not observed a reduction of Benedict's solution by the urine of normal rabbits or guinea-pigs.

I have used the Benedict test for the urines of over a hundred cats, the number of specimens examined amounting to many thousand, and have never found a reduction in the case of any normal animal. The diet was generally horsemeat, sometimes with milk. The highly concentrated urine of starved cats may give an atypical turbidity. In one cat, subject to peculiar paraplegic attacks, a slight reducing property of the urine appeared with each attack and lasted sometimes for a number of days; but the reducing substance was apparently not dextrose, and I did not determine its nature.

The most marked deviation from the rule is presented by the rat. Schwarz is the discoverer of the fact that the urine of normal rats on a diet of bread or rolls acquires strong reducing properties. He found that the reducing substance is completely fermented by yeast, is not precipitated by lead acetate in acid solution, and is dextrorotatory. He could not obtain any definite osazone. By boiling with a mineral acid, dextrose was formed and could be identified by its osazone. He leaves the nature of the excreted sugar undetermined, and calls the phenomenon a mellituria *ex amylo*. His epinephrectomized rats showed it somewhat more markedly than the normal, but it had nothing to do with any reduction of tolerance for pure dextrose. I stumbled upon the same phenomenon before having read Schwarz's paper; it occurred first in a partially depancreatized rat, but controls showed it to be equally marked in normal animals. It may be proper to suggest that the term mellituria *ex amylo* is perhaps not quite accurate. For example, when rats were fed on grain, I have not seen mellituria. If starch has anything to do with it, it would appear to be only cooked starch. My own notion has been that the dextrins of bread or rolls are the substances essentially concerned; that they may perhaps be absorbed in the form of some poorly assimilable sugar, or perhaps in the form of dextrin itself, which reaching the

kidney may be broken down into sugar as in the case of parenterally injected dextrin in other species.

The animal in which the occurrence of a slight glycosuria under laboratory conditions is most important is the dog. The degree is, in rare instances, sufficient to cause unmistakable reduction of Fehling's and other copper reagents, and to permit identification of the dextrose present by the usual fermentation, polariscopic and phenylhydrazine methods. The condition is rare, and the cause is unknown. Biedl (1) investigated the urine of 155 dogs, and found glycosuria twice. Eber (ref. by Rosenberger, p. 331) in 20,427 cases found spontaneous glycosuria twelve times; the glycosuric animals were of the "small, idle" sort, leading luxurious lives. Such animals are subject to diabetes. Canine glycosuria is probably never normal; there is a possibility that tainted meat or some slight digestive disorder of the dog may be at the bottom of it. The non-diabetic form has nothing to do with carbohydrate diet; in fact, out of the three or four instances in which I have observed it, only one of the animals was receiving any carbohydrate. It may be present on meat diet and disappear on bread diet. The trace of glycosuria may conceivably result from some trivial fault of the kidney, perhaps some slight failure of the tubules to resorb part of the sugar which the glomeruli excrete, or something else equally unimportant. The important thing is that it does not represent an increased permeability of the kidney for sugar in any true sense of the word, nor any lowering of the animal's assimilation limit for any form of carbohydrate. In a dog with a genuine lowering of sugar-tolerance, caused by partial pancreatectomy, prolonged starvation, or any other cause whatever, a subcutaneous dextrose injection of 2 to 5 g. per kilo will produce glycosuria. In a dog with the anomalous form of glycosuria mentioned, such an injection will often cause a disappearance of reducing substance from the urine for the ensuing hours or days. In one such animal also (Dog 17), weighing 8420 g., I gave an intravenous injection of 3 g. dextrose while this condition was in progress. The reducing substance in the urine was titrated as dextrose, and assumed to be such on the basis of typical osazone formation and fermentation by Saccharomyces apiculatus; no polariscopic tests. The excretion on meat diet had been about 0.3 per cent for several days; the subsequent urine-record was:

Date.	Quantity, cubic centimeters.	Sugar, per cent.	Sugar, grams.
Nov. 9.....	200	0.33	0.66
	Intravenous injection as stated		
Nov. 10.....	260	0.29	0.75
Nov. 11.....	285	0.	0.

One other dog in the laboratory showed the same rare condition at the same time, thus throwing a little suspicion upon the meat or some common cause. Dog 21 from February 16 to 21 also showed occasional traces of reducing substance. Close confinement may have been the cause. Yet on the morning of February 17, 10 g. dextrose per kilo was given by stomach-tube, fasting; the measurable excretion was only 0.08 g., and the 5 p.m. urine was non-reducing.

Pflüger encountered a phenomenon of this sort in a few dogs. In most instances, it amounted only to an occasional "green reaction" with the Worm-Müller test. Objections to the Worm-Müller method are stated in the text of Hammarsten (p. 759). Some of the reactions noted by Pflüger were, however, apparently heavy enough to indicate something more than technical error. The animals in question happened to be certain ones which had undergone extirpation of the duodenum. The occasional coming and going of these traces of glycosuria was looked upon by Pflüger as a "periodical diabetic disposition," and was attributed to "the battle of antagonistic forces which govern carbohydrate metabolism," and so forth. The dogs in fact had no symptoms of diabetes, nor any lowering of their normal carbohydrate tolerance. Dog I [see Pflüger (21), pp. 8–9] never showed a trace of spontaneous glycosuria. Dog II [Pflüger, l. c., pp. 10–11] distinctly showed the peculiarity mentioned above, viz.: the presence of a trace of glycosuria when no carbohydrate was being fed, and its absolute disappearance when carbohydrate was added to the diet. The glycosuria of 1.045 per cent in this 9-kilo dog, after 100 g. dextrose by mouth, demonstrated a normal tolerance. Dog III [Pflüger, l. c., pp. 12–13] showed a bare trace of spontaneous glycosuria for a few days following his duodenal operation. Then this 12-kilo dog took 200 g. dextrose by mouth without a trace of glycosuria, and with 275 g. dextrose excreted only a trace.

At the present time, we know that "duodenal diabetes" has no existence. Pflüger's dogs represent animals slightly abnormal by reason of a non-specific operation and the generally unfavorable influence of laboratory conditions, and illustrate the tendency of dogs in sporadic instances as a result of some slight anomaly to excrete a perceptible trifle of glucose in the urine. The condition is rare, transitory, and without significance, and requires mention only that those who chance to meet it may be forewarned.

7. Other Channels of Sugar Excretion.

Before taking up the wider subject of glycosuria, a few statements concerning the appearance of sugar in other secretions or excretions are proper. Von Noorden [(1), pp. 151–53] gives doubtful assent to the possible presence of sugar in the saliva and sweat of some diabetics. Naunyn (p. 237) speaks in a similar tone concerning its reported presence in sweat and tears. The frequency of cases of this sort, and the quantity of sugar alleged to be thus atypically excreted, have diminished apparently to zero as methods and observations have become more exact. The highest figure is that of Fletcher, quoted by Naunyn, who estimated that his patient's skin gave off 170 g. of sugar in 24 hours. Other early reports of this nature likewise contain high estimates. But neither Naunyn nor von Noorden has ever personally seen such a case, and there seems to be in all the more recent literature no instance reported of sugar in tears, saliva, or sweat. I have tested the saliva of diabetic dogs, also the saliva of those glycosuric as a result of sugar-injections, piqûre, or phloridzin, and furthermore of combined cases, *i.e.*, dogs which in addition to diabetes or piqûre or phloridzin had received considerable sugar-injections; and in no case has the saliva contained any trace of sugar. The gastric juice is regularly sugar-free in diabetes. The presence of small amounts of sugar in the cerebro-spinal fluid is well-known, not only in diabetes but in some cases of disease of the nervous system without diabetes. Increase of sugar in the aqueous humor has been proposed as a convenient index of hyperglycemia in rabbits [Kahn — used also by Starkenstein (3)]. But these fluids belong more properly with the lymph.

Rössler reported that normal human feces contain no sugar, but that it may be found in demonstrable quantity in diabetic feces, and can be increased by feeding dextrose or lactose. He gives references to the few writers who before him found sugar in

diabetic feces. Kossa (2) states that chickens which have received intramuscular injections of phloridzin excrete sugar both in the urine and in the feces. Apparently the first observation of intestinal excretion of sugar in normal animals was that of J. B. MacCallum (ref. by Fischer and Moore), who noted it after morphine and after intravenous injection of $m/6$ NaCl solution in rabbits. Fischer and Moore failed to find this "intestinal diabetes" in connection with the glycosuria produced by piqûre, by morphine hypodermically, or by slow injections of $m/2$ dextrose or saccharose solutions intravenously; though in such cases the excess of blood-sugar does pass into the peritoneal fluid. When, in addition to the above treatment, sodium chloride is injected intravenously, a slight intestinal excretion of sugar occurs. These authors believe the result due to altered permeability of the cells of the intestinal mucosa caused by NaCl.

A recent, careful study of the question is that of Kleiner, in Meltzer's laboratory. He kept rabbits on the table for an hour or more, with a strong dextrose solution flowing into the jugular vein; and in some of the animals a double nephrectomy had been done on the day previous. His preliminary analyses showed that the contents of the stomach and intestine of normal rabbits on carbohydrate-poor diet contain barely measurable traces of reducing substance. By massive intravenous injections (up to 7 g. per kilo, in 20 per cent concentration) there was a definite but insignificant increase of the above traces; an average of only 0.1 g. increase in the stomach and 0.15 g. increase in the intestine. A preceding double nephrectomy caused the increase to be a fraction greater; an average of 0.15 g. increase in the stomach and 0.24 g. increase in the intestine. The author "prefers not to draw the definite conclusion, that in living animals dextrose is eliminated normally into the intestine." He rejects the notions of "vicarious action" of the intestine, and of "intestinal diabetes."

A research evidently synchronous with that of Kleiner is by Grigaut and Richet, who call attention to the reported elimination of urea and chlorides by the bowel in certain conditions; also to a previous statement by Rénon and themselves, that the diarrhea of diabetics is frequently accompanied by an intense elimination of glucose, a condition which they named "glycosentérie." Their present paper reports observations upon the comparative intestinal and renal elimination of urea, chlorides, and dextrose, in normal dogs anæsthetized with chloralose. In three

animals of respectively 6, 7, and 8 kilos weight, they gave intravenous injections, in 25 per cent solution, of respectively 162 g., 112 g., and 160 g. dextrose; and they found gastro-intestinal elimination of respectively 1.05 g., 3.5 g., and 10.2 g., compared with a renal elimination of respectively 14 g., 11 g., and 14.6 g. Within the brief limits of a *Comptes rendus* article, they give no details of their technique, nor anything upon which their truly extraordinary findings can be judged. The enormous dosage, which in itself might affect the intestinal permeability, may possibly be the explanation.

In the few tests which I have made, sugar has not been found in the feces of diabetic dogs, nor in normal animals receiving dextrose by mouth, even when the doses were large and when considerable diarrhea resulted. After large doses of dextrose by mouth, there has been apparently a large loss of sugar through the feces in three cases, all of them abnormal. Dog 18 had diarrhea in consequence of repeated doses of phloridzin by mouth; on April 9, a dose of 8 g. dextrose per kilo of body-weight was given by mouth, and the diarrheal feces were heavy with sugar. Dog 58, on June 14, was subjected to Bernard puncture, and later given 10 g. dextrose per kilo by mouth. Owing to the well-known disturbances of absorption resulting from piqûre, the liquid feces contained 9.1 per cent dextrose. Dog 32 was a partially depancreatized, non-diabetic dog, with poor digestion owing to lack of pancreatic juice. On May 1, about 8 g. dextrose per kilo was given by mouth, and the diarrheal feces were heavy with sugar. This example indicates the untrustworthiness of oral tests of the tolerance in animals after pancreatic operations or other operations which may influence absorption; for whether actual fecal excretion of sugar occurs or not, the impaired absorption obviously spoils accurate comparison with normal animals.

An exceptional instance is that of Dog 28. On March 28, this normal animal received a subcutaneous injection of 10 g. dextrose per kilo, and simultaneously an intraperitoneal injection of 5 g. dextrose per kilo. The glycosuria was relatively slight, but the diarrheal feces showed a reduction corresponding to 5 per cent dextrose. In other animals with larger intraperitoneal injections (without subcutaneous injection) the feces have been non-reducing. It is difficult to understand how the large blunt cannula used for injecting Dog 28 could have penetrated a dog's tough intestine, especially since a later laparotomy in this animal showed the

peritoneal cavity free from adhesions. The case is mentioned as an exception.

Tests comparing the intestinal excretion of dextrose in diabetic animals with that of normal animals after dextrose injections might contribute some evidence concerning the question of "free" or "combined" blood-sugar in diabetes.

8. Sugar-Tolerance and its Tests.

Sugar-tolerance is a convenient, though somewhat ill-chosen, expression to denote the upper limit of complete assimilation of sugar, the threshold dosage at which it barely begins to appear in the urine.

In a strict sense, no fixed standard exists. In addition to the ordinary variations as respects kind of sugar, species of animal, mode of administration, and conditions of health or disease, there are other less obvious differences. The normal tolerance of a given species cannot be set at a fixed figure, but only as a rather indefinite value varying between rather distant extremes. The difference between large and small individuals of the same species is one disturbing factor. Yet the tolerance cannot be calculated on a basis of weight, for obesity and like conditions here enter in; and even where the bodily state is considered "normal," who shall figure the possible differences in amount of fat, bone, and other "inactive" tissues, as compared with the weight of muscle, glands, and other highly "active" tissues? And furthermore, when one has carefully determined the exact tolerance of a given individual at a given weight, it may be found subsequently that the same individual at the same weight and under apparently the same conditions shows a somewhat different tolerance. It has been proved that adrenalin cannot be depended upon to produce by the same dose in the same animal on different occasions the same glycosuria. In less degree, the statement is true for sugar. Habituation does not occur.

More important and confusing is the difficulty of deciding just when the limit of assimilation has been reached. It may be supposed that when after a given dose a slight trace of sugar appears in the urine, the point of tolerance has been established; especially if it is further found that a repetition of the same dose again produces the slight glycosuria, and that a slightly smaller dose does not produce it. The results of such a procedure would appear to be accurate and above criticism. But Schlesinger (1)

has correctly noted that the appearance of a mere trace of sugar in the urine may have nothing to do with the sugar-tolerance in any proper sense of the word. The observation of Raphael, that patients sometimes appear to assimilate large doses of sugar better than smaller doses, may be interpreted to the same effect. Naunyn advises that faint traces be ignored in assimilation tests. It is a fact that animals will occasionally show slight glycosuria from a relatively small dose of dextrose, and after a considerably larger dose show less glycosuria or none at all. Schlesinger's observations were with the feeding of sugar. The same is possible, though probably less frequent, with subcutaneous tests. This atypical glycosuria, in a dog with really normal assimilative power, may be illustrated by Dog 21. The facts concerning this dog can be summarized as follows.

On December 20, after fasting 3 days, subcutaneous injection of 3 g. dextrose per kilo caused glycosuria of 0.54 per cent.

On December 30, after fasting 13 days, subcutaneous injection of 7 g. dextrose per kilo caused glycosuria which both in percentage and in amount excreted was less than the above.

On January 1, the dog being now weak from starvation, 3.5 g. dextrose per kilo was given by mouth as a test for hunger-glycosuria. No glycosuria occurred.

On February 17, the dog, in well-nourished condition, received 10 g. dextrose per kilo on an empty stomach. During the preceding 24 hours there had been a slight spontaneous glycosuria. The total excretion from the 62.5 g. of sugar was 0.08 g.

On April 7, subcutaneous injection of 1 g. dextrose per kilo produced no glycosuria.

On April 10, subcutaneous injection of 2 g. dextrose per kilo caused a faint reduction in the urine both of that evening and of the following morning.

On April 13, another injection of 2 g. per kilo caused no glycosuria.

On April 17, subcutaneous injection of 3 g. dextrose per kilo caused a faint reaction only in the urine of that evening.

On April 20, subcutaneous injection of 4 g. dextrose per kilo caused no glycosuria.

On April 25, subcutaneous injection of 5 g. dextrose per kilo caused a barely perceptible reaction in the evening urine.

On June 22, subcutaneous injection of less than 4 g. per kilo caused a faint reaction in the 1 p.m. urine.

This is a dog with normal carbohydrate assimilation. To say that 2, 3, or .4 g. per kilo is the animal's limit of tolerance for dextrose, that is, that the tolerance is only a fraction of the normal, would convey an entirely wrong impression. The dog excreted less after 7 g. than after 3 g. per kilo; it was refractory to hunger-glycosuria; it excreted only 0.08 g. of sugar after receiving 10 g. per kilo on an empty stomach; the dog is normal and has a normal sugar-tolerance.

In a series of cats, I undertook to determine the exact subcutaneous tolerance by means of graded injections every other day. The method is perhaps open to objection, for repetition at such intervals seems to affect the tolerance slightly. They were all on fixed diet under constant surroundings.

Cat 26 (weight 2700 g.) received increasing doses of dextrose subcutaneously every other day, beginning with a dose of 3 g. on October 19. The smaller doses caused no glycosuria. With the larger ones, the following is observable:

10 g. dextrose produced no glycosuria.

11 g. dextrose produced glycosuria of 0.85 per cent. Repeated, it caused no glycosuria.

12 g. dextrose caused glycosuria of 0.48 per cent or 0.72 g. Repeated, its result was 0.57 per cent or 0.54 g.

Thereafter, 11 g. dextrose caused glycosuria of 0.9 per cent or 0.8 g.

Next, 10 g. dextrose, formerly negative, caused the highest glycosuria of all, 1.2 per cent or 0.9 g.

Finally, 9 g. dextrose caused a trace of glycosuria.

The case of Cat 46 (weight 4 kilos; fat) was similar. On February 13, the subcutaneous injection of 15 g. dextrose caused a heavier reaction, in a greater volume of urine, than the injection of 17.5 g. on February 15. On February 19, 10 g. dextrose produced a faint glycosuria, and on February 21 it produced none.

In the case of Cat 70 (weight $2\frac{1}{2}$ kilos), a subcutaneous injection of 8 g. dextrose produced slight glycosuria; a few days later it produced none; but later, an injection of 9 g. caused well-marked glycosuria, proving the tolerance to be between 8 and 9 g.

In any given animal, it is generally possible to fix the subcutaneous tolerance rather closely.

9. Glucose-Tolerance of Different Species.

Although mathematical exactness is impossible, as has been explained, yet it is possible to establish for each animal-species

something like a normal sugar-tolerance, which at least conveys a general idea and is approximately correct for the great majority of individuals. Some attention may profitably be given to a general comparison of the assimilation-limits of man and the common laboratory animals for the most important physiological sugar, glucose.

We may conveniently consider a list of the different species arranged inversely to their powers of sugar-assimilation; that is, with the species of lowest assimilation at the top of the column and those with the highest assimilation at the bottom. Such a series will be made up about as follows:

Frog.
Man.
Guinea-pig.
Cat.
Rat.
Dog.
Rabbit.
{ Birds. }
{ Selachians. }

The hopelessly irregular and bizarre arrangement in this series, as respects position in the animal scale, is apparent.

The frog receives its low rating essentially on the basis of the table published by Sachs [(1), p. 92], who also refers to earlier work of Strauss. From the figures of this table, it is impossible to place the subcutaneous assimilation-limit of the frog for dextrose above 1 g. per kilo at the very highest; and for the most part it falls below, and often very far below, this figure; for example, in the case of a frog of 113 g. weight, glycosuria resulted from a dose of 0.032 g. dextrose; and in one of 105 g. weight, glycosuria occurred after 0.04 g. dextrose. The tolerance in these cases was therefore below $\frac{1}{3}$ or $\frac{1}{2}$ g. per kilo. In fact, the lower limit was not established; for no matter how small the dose, a trace of glycosuria resulted in every animal except one. Since this one, weighing 90 g., received 0.1 g. dextrose without glycosuria, the possibility of marked individual differences is suggested. It is highly probable that complete investigation would show that the frog's sugar-tolerance varies with season, temperature, and different metabolic conditions. The low tolerance stands in interesting contrast with the high normal blood-sugar.

The common test for alimentary glycosuria in man is the administration of 100 g. of pure dextrose. A human being who can fully assimilate this quantity is considered normal. Yet most persons are able to assimilate more than this arbitrary amount; and if 100 g. be set as the lower normal limit, 250 g. may probably be considered the upper normal limit. By subcutaneous injection, which is a more accurate method, Voit (2) observed traces in the urine after injection of 60 g.; and, after injection of 100 g., a glycosuria lasting $7\frac{1}{4}$ hours and involving excretion of 2.64 g. Achard and Weil [ref. by Lepine (1), p. 234] state 40 or 50 g. as the limit which can generally be injected subcutaneously into a healthy person without producing glycosuria. On the basis of these facts, we must place man as the lowest in rank among known mammals as respects his powers of sugar-assimilation. The human tolerance by mouth must be figured as probably between 2 and 4 g. per kilo, with possible slight variations in either direction. The figures yielded by the subcutaneous experiments represent a tolerance between 1 and $1\frac{1}{2}$ g. per kilo.

The guinea-pig is next above man. Frugoni and Stradiotti fixed the "threshold" dose subcutaneously at 3 g. per kilo. Marrassini (4) gave dextrose by mouth, the doses being about 10 g. in pigs weighing 500–975 g. As the doses were not given fasting, and as the author's purpose was to produce considerable glycosuria, these experiments do not necessarily disagree with those of the above authors. Süssenguth (2) injected guinea-pigs subcutaneously with doses of 5 to 10 g. per kilo, and obtained glycosuria. Since the glycosuria was slight, his pigs would seem to have had a higher tolerance than those of Frugoni and Stradiotti.

In a series of guinea-pigs weighing 700–900 g., I obtained the following results with subcutaneous injection of Kahlbaum dextrose in 10 per cent solution. The pigs were taken from feeding, injected, and isolated in small metabolism cages without food for the ensuing 12 hours, to obtain uncontaminated urine.

Number of pig.	Number of grams dextrose per kilo.	Benedict test of urine.
1	5	Heavy.
2	4	Moderate.
3	3	Slight to moderate.
4	2	Slight.
5	$1\frac{1}{2}$	Negative.
6	1	Faint.
7	$\frac{1}{2}$	Negative.

The reaction in Pig 6 is probably to be interpreted as an accidental trace, so that the true threshold dose is about 2 g. per kilo. By comparison with the findings of other authors, it may be judged that differences are possible between different strains of guinea-pigs, but the general tolerance of the species is low.

Next above the typical herbivore, the guinea-pig, stands the typical carnivore, the cat. The literature seems to contain nothing definite concerning its assimilation limits. Tests by oral administration would be unreliable, because the animal not only vomits very readily, but also may on occasion hold the dose for hours in its stomach. For subcutaneous injections the cat is ideal, and in no other species is the tolerance more definite and reliable, or the injections better borne. In numerous experiments I have determined that the subcutaneous limit for the cat lies generally between 3 and 4 g. per kilo, though in a few cats it may be slightly above 4 g. per kilo.

The rat stands next above the cat, though observations in the literature are lacking. Schwarz stated that his epinephrectomized rats died promptly upon the feeding of 0.4 g. dextrose, but that normal rats burn 1 g. completely. Since Schwarz's rats mostly weighed between 100 and 200 g., this would indicate an oral assimilation of somewhere between 5 and 10 g. per kilo.

The brown-and-white or black-and-white rats, which I have used, have a subcutaneous dextrose-tolerance barely above 5 g. per kilo. Injection of $5\frac{1}{2}$ g. per kilo has proved sufficient for glycosuria. Here also, the possibility exists that a certain amount of difference may be found between different varieties.

Concerning the dog, numerous statements exist in the literature, the more recent ones of which are approximately harmonious and correct. Hofmeister (1) — the author of the phrase "assimilation-limit" — cites the earlier authors, and he himself obtained values which were too low, and which have been a disturbing element in the literature of the subject. Working entirely with oral administration, the highest figure he ever found was 5.8 g. per kilo, and just below this was another dog with 5 g. per kilo. But he also obtained the impossibly low value of 1.3 g. per kilo, and the majority of the results range between 2 and 3 g. per kilo. They are called impossible, because they convey an entirely erroneous impression of a dog's power of sugar assimilation, and they lie even below the limits of subcutaneous tolerance, which in turn are always lower than the true oral tolerance. Pflüger (21) puz-

zled over Hofmeister's results considerably, and satisfied himself that the administration of the sugar dissolved in large quantities of liquid and on an empty stomach was an important factor. Pflüger's own results seem correct. His Dog I [Pflüger (21), pp. 8 and 9] took over 16 g. dextrose per kilo by mouth, along with food, without glycosuria. His Dog II showed slight glycosuria after about 11 g. per kilo with food. His Dog III (pp. 12–13) showed no glycosuria after 15 g. per kilo with food, and only a "green reaction" after about 18 g. per kilo. These were cases of nothing but duodenal extirpation, therefore normal tolerance. His results with perfectly normal dogs are tabulated by Pflüger [(21), p. 21]; a tolerance of 11.5 or 12.1 g. per kilo when the sugar was given with meat stew, and less than 8 g. per kilo when it was given in soup. Pratt and Spooner found the oral assimilation limit to be about $11\frac{1}{2}$ g. per kilo. Schlesinger (1) draws distinctions between large and small dogs regarding assimilation limits, even when reckoned per kilo. Large dogs can dispose of more sugar per kilo than small dogs. His dogs of 5 kilos had threshold-limits of 40 to 50 g. by mouth. His dogs of 7 or 8 kilos often took 70 or 80 g. without glycosuria.

Altogether, Hofmeister's low results can be fully explained by the following factors:

(1) Unusually small dogs (2 or 3 kilos).
(2) Poor nutrition of some dogs.
(3) Administration on empty stomach.
(4) Solution of sugar in large quantities of liquid.
(5) Possible influences of salts and extractives of the large volume of soup, since salts lower sugar-tolerance. Possibly the salt-content of Hofmeister's soup was high.
(6) Acceptance of mere traces of glycosuria as evidence that the limit has been reached.

Boeri and de Andreis have published observations on this subject. Zanda (2 and 3) has lately tested the oral assimilation of dogs and found it high. One of the best discussions concerning both alimentary glycosuria in general and that of dogs in particular, with the literature of the subject, is contributed by De Filippi (1). He rightly points out the widely different values obtained by giving sugar pure, on an empty stomach, or with food. He publishes results obtained by Quarta, making a wide distinction between the sexes; an average tolerance of 4.06 g. per

kilo for male dogs and of 10.28 g. per kilo for females. De Filippi's own experiments show an assimilation of from 8.16 g. to 10 g. per kilo, fasting, without glycosuria. It is important to emphasize, as De Filippi has done, that uniform results can never be achieved except by uniform methods. This applies to tests of human tolerance as forcibly as in the case of dogs. Uniform methods must include an empty stomach (preferably a fixed number of hours after the last meal; perhaps regularly in the morning before breakfast), the use of pure sugar, a fixed quantity of water to dissolve or accompany the sugar, the avoidance of all food (including soup), and the avoidance of drugs.

My own administration of sugar orally to dogs has never been for the purpose of establishing any precise limits of tolerance; and, at the most, comparisons have involved only how the same dog would react to the same dose at different times, and the dose has ordinarily been chosen high enough to cause well-marked glycosuria. The assimilation of commercial glucose is not identical with that of the purified article; probably the contained salts lower the tolerance a trifle. The following incidental observations illustrate this point. All the doses were given fasting, and all were commercial glucose with the exception of Dog 18.

Number of dog.	Date.	Grams of dextrose per kilo.	Glycosuria.
18	Aug. 5	15	{ 1.7 per cent { 2.1 per cent
20	Dec. 6	18	Heavy
28	Jan. 17	5	0
38	June 6	15	7.3 per cent
58	June 6	15	9 per cent
60 B	June 6	15	4.5 per cent

The subcutaneous injections of J. Scott and others proved that dogs readily dispose of large doses of dextrose injected subcutaneously. Knowledge of the subject was advanced by the study of Underhill and Closson (3); and Underhill and Hilditch used the subcutaneous injection of 5 g. dextrose per kilo as a test for lowering of carbohydrate tolerance. The test is to be commended, for it is an accurate mode of administering sugar, and the amount chosen never (barring the accidental traces heretofore mentioned) produces glycosuria in any normal dog.

In numerous subcutaneous injections in dogs, I have found that the assimilation capacity is generally in the neighborhood of 8 g. per kilo, varying from 7 to 9 g. Slight exceptions in either direction are possible but unusual.

The rabbit seems entitled to a position above the dog, and, accordingly, to the highest rank among all mammals that have been investigated as respects assimilation of sugar. The eccentricities of the rabbit nature must be considered in all experiments. Thus Becker [ref. by Hofmeister (1)] claimed distinct glycosuria in 5 out of 30 rabbits after intrastomachal injection of 0.22 to 0.962 g. dextrose. These injections might just as well have been water. The rabbit is liable to traumatic and emotional glycosurias, and that is the sort which Becker's intrastomachal manipulations evidently produced. More recently Frugoni and Stradiotti (1 and 2) placed the "threshold dose" for rabbits subcutaneously at 2.35 g. per kilo, as compared with 3 g. per kilo for the guinea-pig; and they suggested the large islands of Langerhans of the guinea-pig's pancreas as the basis for its superior sugar-tolerance. Ascoli and others have considered the suggestion interesting. But the suggestion is far from corresponding to the facts. The guinea-pig, with its numerous giant islets, is at the foot of the list of laboratory mammals in its power of sugar-assimilation. The low values obtained by these authors for the rabbit are atypical. Zanda (2) has also formed the opinion that the tolerance of the rabbit is very low. The differences are too wide to be explained as differences between strains or varieties of rabbits (though the low values are all from Italy). It is barely possible that the oral tolerance of the rabbit may be lower than its subcutaneous tolerance. Throughout all species, notwithstanding the differences in the digestive, circulatory and other organs, the oral and subcutaneous tolerance seem to run approximately parallel, the latter always somewhat below the former. The rabbit might constitute an exception. But that this is not the explanation is indicated by the fact that Frugoni and Stradiotti's small doses were given subcutaneously, while some of Fichtenmayer's large doses were given by month. Traumatic, emotional, or other disturbing influences are probably the explanation, in a highly erratic and uncertain animal.

Süssenguth (2) injected into rabbits subcutaneously, through a period of days, dextrose in doses of 5 to 10 g. per kilo, and with the larger doses observed glycosuria of 0.3 to 2.3 per cent. The

higher percentages probably were obtained toward the close, when his rabbits were sick.

Marrassini (4) gave dextrose to rabbits by mouth, and (1) also subcutaneously. Glycosuria generally appeared after subcutaneous doses of 15 to 20 g., which may be supposed to indicate something like 10 g. per kilo.

Heilner (1) gave dextrose orally and subcutaneously during fasting. The oral doses of approximately 31 g. caused sometimes a very slight glycosuria, sometimes none. His rabbits weighed nearly 3 kilos at the outset of starvation, and about $2\frac{1}{2}$ kilos on the day of injection. The doses represent something like 12 or 13 g. per kilo, and, as they were given on the fourth day of fasting, the tolerance is obviously high. Similar (or the same) rabbits received similar doses subcutaneously. Some of them showed slight glycosuria, and some showed none. The most curious feature is that one rabbit which received 49.832 g. subcutaneously showed no trace of glycosuria. There was no albumin in the urine.

Fichtenmayer's tables will be found reproduced in Chapter IV. He gave rabbits, sometimes after long starvation, dextrose by mouth or subcutaneously. Some of the results may be roughly summarized as follows.

EXPERIMENT IV: *By Mouth.*

About	10 g.	per kilo	on	4th	day of starvation,	no glycosuria.
"	14 g.	"	"	7th	" "	positive glycosuria.

EXPERIMENT VI:

"	14 g.	"	"	7th	" "	no glycosuria.
"	17 g.	"	"	8th	" "	slight gylcosuria.

EXPERIMENT VIII:

"	12 g.	"	"	7th	" "	no glycosuria.

EXPERIMENT IX: *Subcutaneously.*

About	16 g.	per kilo	on	4th	day of starvation,	no glycosuria.
"	33 g.	"	"	5th	" "	2.2 per cent glycosuria.
"	21 g.	"	"	7th	" "	no glycosuria.
"	35 g.	"	"	8th	" "	1.8 per cent glycosuria.
"	23 g.	"	"	9th	" "	1 per cent glycosuria.

EXPERIMENT X:

About	21 g.	per kilo	on	4th	day of starvation,	6.2 per cent glycosuria.
"	21 g.	"	"	5th	" "	no glycosuria.
"	21 g.	"	"	6th	" "	no glycosuria.
"	21 g.	"	"	7th	" "	no glycosuria.
"	22 g.	"	"	8th	" "	no glycosuria.
"	23 g.	"	"	9th	" "	no glycosuria.
"	22 g.	"	"	10th	" "	0.8 per cent glycosuria.
"	22 g.	"	"	11th	" "	no glycosuria.

Throughout this last experiment, the actual dose was constantly 30 g. The loss of weight causes in all the experiments an increase of the dosage as reckoned per kilo, but this is fair, especially in view of the lowering of assimilation generally caused by inanition. Even if all doses be reckoned on the animal's initial weight, the tolerance in Fichtenmayer's experiments is still enormous. The facts that on the same dosage glycosuria may appear and disappear, and that the subcutaneous tolerance is higher than the oral, raise a question as to whether we are here dealing with a normal phenomenon, or with some eccentricity of the rabbits, perhaps a change in the permeability of their sensitive kidneys.

Some of my tests of the subcutaneous tolerance in rabbits are as follows.

Number of Rabbit	"Normal" Weight, Kilos	Date	G. Dextrose Per Kilo	Glycosuria
32	.2	May 7	6.	0
34	1.6	August 17	2.5	0
"		" 19	3.75	0
"		" 21	5.	0
"		" 23	9.4	Slight
"		" 25	9.4	*Heavy
40	1.3	" 15	3.	0
"		" 17	4.6	0
"		" 20	6.	0
"		" 22	7.7	0
41	0.94	" 30	16.	Heavy
42	1.8	" 30	8.3	Moderate
43	1.1	" 30	14.	Moderate
50	2.5	May 15	5.	1.2%
"		" 18	5.	0.42%

*Rabbit in weakened condition.

My experiments, therefore, show a considerable variation, but tend to place this strain of rabbits not above the dog, and if anything below it. I have assigned the rabbit its high position in the

scale of tolerance on the basis of the reports of others, especially Heilner and Fichtenmayer. It is a variable animal.

Kausch found it practically impossible to produce alimentary glycosuria in birds (ducks). His table [see Kausch (1), pp. 300–301] shows a few exceptions to this rule, even a glycosuria of 5.7 per cent (excretion 1.2 g.). But he himself draws the conclusion that alimentary glycosuria in ducks is practically impossible. Even with doses of 20 g. per kilo, the urine may show no sugar, the feces being also sugar-free. If too much sugar is given, it merely flows off in the feces. The reason for the condition is that the kidney of birds is highly impermeable to sugar. Complete extirpation of the pancreas, except in birds of prey, generally causes no glycosuria, though, as Kausch showed, the blood-sugar may reach even 0.7 per cent. The work of Giaja is of interest in this connection; he produced glycosuria in chickens with relatively small intravenous injections of dextrose; this glycosuria occurred when the blood-sugar reached 0.25 per cent; but in depancreatized chickens, blood-sugar of 0.29 per cent caused no glycosuria. It is desirable that the subcutaneous tolerance should be determined. Kossa's work would seem to discourage the investigation; for he found 20 g. per kilo subcutaneously to be a fatal dose, and even 10 g. per kilo, which most mammals tolerate well, produces in chickens and pigeons a dangerous and characteristic collapse. But Süssenguth failed to confirm these observations; and it seems probable that large doses of sugar may be tolerated by birds if given in dilute solution.

Nothing is known concerning the relative tolerance in birds and selachians. Diamare has shown that the kidney of selachians is highly impermeable to sugar. In Scyllium catulus, pancreas-extirpation produced no glycosuria, though the blood-sugar reached 0.145 per cent. By subcutaneous or intramuscular administration of dextrose he failed to produce glycosuria, though the blood-sugar was raised to 0.26 per cent. Glycosuria was caused only by intravenous injections of sugar.

The behavior of the selachian kidney possesses a certain theoretical interest. It is a fact that the mammalian or human kidney can accustom itself to an increased percentage of blood-sugar, and excrete no sugar even in the presence of prolonged hyperglycemia. The normal kidney also tolerates the normal percentage of blood-sugar without appreciable glycosuria. But habituation of the kidney to sugar is not essential to its imper-

meability for sugar. Thus in the selachians, whose blood normally contains no sugar at all or barely discoverable traces, the impermeability of the kidney for sugar is greater than in mammals or in the frog, which have a normal glycemia.

10. Influences Modifying Sugar-Tolerance.

These may be considered as: (A) General, (B) Special.

(A) General Causes Modifying Tolerance.

Season was found by Stütz to be without influence upon alimentary glycosuria in man. I have observed no differences in animals which suggest any influence of season.

Differences between *strains or varieties* within a given species may possibly be sometimes distinguished, as was suggested concerning rabbits and guinea-pigs; but no such differences have as yet actually been demonstrated. Apparently, no constant differences in the sugar-assimilative powers of different human races are known. My own experience has been chiefly with cats and dogs, and dealing with all sorts and kinds of these animals, I have found no constant variations.

Sex is without influence. Quarta's supposed distinction, published by De Filippi, is a misapprehension, probably depending upon coincidence. His figures for female dogs are normal; those for male dogs are too low. He may have been misled by slight traces of glycosuria, accidental in character and without real significance.

Age is an important factor. Magnus-Levy [(4), p. 437] quotes Aldor as having found a slight reduction of sugar-tolerance in aged human beings. I have had no experience with animals that could be called senile.

Children are credited with a far higher tolerance for sugar than adults. Lepine [(1), p. 213] cites an experiment by Miura, in which a boy weighing 39 kilos ate 430 g. of pure glucose. The total sugar excretion was 1.14 g. It is certain that no adult could take and retain 11 g. per kilo with so little glycosuria. Probably the average adult would show a greater glycosuria if he should take the same actual quantity which the boy took. Finizio (ref. by Rosenberger) found the tolerance as high as 6.5 to 7 g. per kilo at 4 to 6 years. The most careful study of the question is by Greenfield. He found the tolerance in childhood practically independent

of body-weight, state of nutrition, or various states of illness. But it is especially dependent upon the *age*. It rises from 0.4 g. per kilo at 2½ years to 2.8 g. per kilo at 9 years. At the age of 10 the child attains the sugar-tolerance of the adult.

In view of the importance of carbohydrates for the young, and the active nature of their metabolism, a high tolerance might well be expected. But my experience with young animals has been to the contrary.

Kitten 10, aged about 5 weeks, received on July 5 a subcutaneous injection of 30 cc. 10 per cent dextrose, representing about 9 g. per kilo. Glycosuria heavy. Kitten 11 (same litter) received 15 cc. 10 per cent dextrose in the forenoon and 15 cc. in the afternoon; each dose represented about 3.75 g. per kilo. No glycosuria. The former kitten showed glycosuria from a pro-kilo dose which would have caused glycosuria in a grown cat. The latter kitten showed no glycosuria from a pro-kilo dose which would have caused no glycosuria in a grown cat.

Kittens 6, 7, and 8, with initial weights of 332 to 363 g., were fed daily with dextrose solution, generally in divided doses. The total taken by each kitten each day was 2½ g., 5 g., and 7½ g., respectively, corresponding to about 7½ g., 15 g., and 22½ g. per kilo. Notwithstanding the fact that the doses were distributed through the day, all three kittens showed glycosuria.

Pups 1–4B (age 22 days) received the following subcutaneous injections of dextrose in 10 per cent solution.

Number of pup.	Date.	Weight (grams).	Absolute dose of dextrose (grams).	Glycosuria.
1B	Aug. 2	760	2	Slight to moderate.
2B	Aug. 2	920	4	Heavy.
3B	Aug. 3	820	3	Moderate.
4B	Aug. 2	660	1	Faint.

These pups were living comfortably with their mother, in the best possible health and nutrition. Even in the case of Pup 2B, the weight was nearly a kilo, therefore to correspond to the tolerance of a grown animal, the tolerance should have been close to 8 g. But the injection of 4 g. resulted in a very heavy glycosuria. Pup 4B received the lowest dose, an injection of 1 g., which was hardly more than 1½ g. per kilo. Yet a very distinct glycosuria was the result.

Conclusion. — The tolerance of kittens for dextrose is somewhat less than that of grown cats. The tolerance of puppies is only a fraction of that of adult dogs.

(B) Special Influences Modifying Sugar-Tolerance.

The cause of the differences produced by age or other general influences modifying the tolerance is unknown. But the effects of most of the *special* influences affecting the tolerance should be rather definitely classifiable into three groups. The agents in question may conceivably change:

(I) the absorption of the sugar administered,
(II) its utilization by the tissues,
(III) its excretion by the kidneys.

Clear-cut distinctions between the three groups are in some cases impossible, either because of our lack or information, or because the same agent may have more than one effect. But some particular effect is likely to be most important either for a given agent or for the purposes of some particular discussion; and in any event, the conception of the three possible modes of action is useful.

In general, it may be stated that causes which increase the power of assimilation are relatively few, and the increase produced is relatively slight. On the other hand, causes which reduce the limit of assimilation are relatively numerous, and the degree of reduction may be very marked. Without attempting exhaustive discussion or enumeration, we may consider various examples under the classes suggested above.

Concerning (I). — That causes retarding the absorption of a dose of sugar may raise the limit of assimilation, and that causes accelerating the absorption may lower the limit of assimilation, is self-evident. A multitude of influences affecting gastro-intestinal absorption can easily be imagined, and their consideration may profitably be omitted. Agencies affecting absorption in general and bearing upon subcutaneous or intraperitoneal as well as intestinal absorption are few. Adrenalin injections might have an effect. Any lymphagogue or any agent diminishing lymph-formation might be of influence. Weakened circulation undoubtedly delays absorption and must be considered in some experiments; augmented circulation may conceivably hasten absorption. A diminished rate of absorption may be a partial or

complete explanation of the increased sugar-assimilation observed in hypothyroidism or even in adrenal deficiency. Especially in the former condition, sluggish circulation and sluggish processes in the organs and tissues are sufficiently well marked to afford some basis for such an assumption, though changes in the utilization of sugar may also well be imagined.

This is a convenient place to discuss the influence of food. Among many subcutaneous injections given under many conditions, I have never seen any variation that could be attributed to any phase of the gastro-intestinal digestion. Tuckett (2) concluded that food, and carbohydrate food in particular, has no demonstrable effect upon the internal secretion of the pancreas. Recognizing that the tolerance of ingested sugar may be almost doubled by an accompanying meal, authors have universally assumed that the difference is explainable by a mechanical alteration of absorption. When Hofmeister's dogs received sugar in large quantities of soup, absorption was doubtless hastened. When Pflüger's dogs received sugar in meat stew, it is assumed that the meat mechanically held back the sugar from absorption; the entire mass was detained longer in the stomach; after entering the intestine, time was required for the sugar to diffuse out from the interior of the pieces of meat, etc. This sounds entirely plausible; but might it be tested experimentally? Supposing the sugar were soaked up in rags, or in sawdust, or in charcoal, or in agar; supposing it were given along with paraffin oil, or other indifferent substances; would the effect be anything like that of the meat? Are there differences between foods? differences between giving sugar along with starch only, fat only, or protein only? differences between giving it with solid chunks of meat, or with solutions of albumin or peptone? If sugar is given soaked up in hay, will the result be the same in the rabbit, for which hay is a natural food, and in the dog, for which hay is practically a foreign body? If sugar alone or fat alone is fed for a prolonged period, severe disturbances result; but protein alone can be taken indefinitely; why? The same doses of sugar which alone, continued for a week or two, will produce severe gastro-intestinal disturbance, are harmless when given with meat. It is not probable that rags or agar or kieselguhr or fat would thus protect the bowel. Magnus-Levy [(4), p. 158] quotes authors who found that long continuance of a diet too poor in protein gave rise to impaired absorption of all foods, and even to anatomical lesions of the

bowel. Kossa (1) refers to the case of Starck, who, in undertaking to experiment upon himself with a diet of pure sugar, produced a condition which ended in his death. "Osmotic" injury of the bowel should be preventable by other colloids as well as by protein food. Against the hypothesis of bacterial injury may be set the fact that sugar is most quickly absorbed when given alone. Eppinger and Falk have suggested the possibility of a combination of glucose with fatty acids in metabolism. Spiro (2) has brought evidence interpreted in favor of a possible relationship of this sort between carbohydrates and proteins in metabolism; when certain substances are introduced together, the end-products are different than when they are introduced alone. It would appear to be perhaps worth investigation whether the influence of food upon the assimilation of sugar is a mere mechanical matter, or whether it may not probably be something more. It is possible to conceive of combinations of some kind between sugar and other foods, either in the lumen or in the wall of the intestine.

Concerning (II).—Causes increasing utilization are, as stated, comparatively few, and their action comparatively slight. In harmony with the observations of Pflüger (2) concerning the general increase of combustion attending high temperature, several authors have found specifically an increase of the power of sugar assimilation as a result of elevation of the body-temperature. Grober, and also Stütz, working with alimentary glycosuria in man, found that elevation of temperature raises the limit of assimilation. Hohlweg and Voit considered tests with dextrose or levulose unpromising, on account of the normally high assimilation and low excretion. They therefore employed subcutaneous injections of the less easily oxidizable sugars, galactose, maltose, saccharose, and lactose. Rabbits in superheated cages showed a well-defined increase of utilization of the first three, but lactose continued to be practically quantitatively excreted. The possibility presents itself that one reason for the high assimilation limit of the rabbit for sugar may be its normally high temperature, and the ease with which it generally reacts to sugar-administration with temperatures which in most species would be hyperpyrexia. (105–106° F. in some of my rabbits.) The fact that this temperature is higher after subcutaneous than after oral administration might possibly assist in explaining the higher tolerance of Fichtenmayer's rabbits after the former than after the latter mode.

The tendency to alimentary glycosuria in fever patients is not really an exception to this law. Poll in 1896 reported the ease with which glycosuria *e saccharo* can be produced in fever. Richter in 1898 tried to imitate the condition in rabbits by puncture of the corpus striatum. But in the resulting fever, the administration of 20 g. dextrose generally failed to cause glycosuria. He attributed his failure to the brief duration of the hyperthermia. But unless complicated by the nervous lesion, this or any other aseptic fever properly increases tolerance. The so-called febrile glycosuria is really a toxic glycosuria. Not the fever, but the intoxication facilitates glycosuria. Pyrexia per se increases the tolerance of sugar, perhaps to slight extent by rendering the kidneys less permeable, but chiefly by increasing utilization in the tissues.

Grober, also Stütz, found the sugar-tolerance in man increased by muscular exercise. Comessatti (1) reviews the publications showing that dextrose-perfusions increase the working-power of muscle; and proves the converse, that muscular work increases the utilization of dextrose. His rabbits could by work in a tread-mill be made to endure 20 per cent more dextrose than the normal without glycosuria, the test being Blumenthal's standard, the minimum quantity that produces glycosuria in a 5-minute intravenous injection. The assimilation of levulose and galactose was increased in smaller degree. Hohlweg's work with muscular exercise is a continuation of that of Hohlweg and Voit with overheating. By the exercise, a dog was made to utilize increased quantities of galactose, maltose, and saccharose, but lactose continued to be quantitatively excreted.

These two are the only important influences increasing sugar-utilization by the tissues in the normal organism. Among pathological conditions are some, notably hypothyroidism, adrenal deficiency, and certain hypophyseal disorders, which increase sugar-assimilation, quite possibly by affecting its utilization in the tissues. There is no known disorder or condition of the pancreas which increases the tolerance for sugar.

The condition in which sugar-utilization in the tissues is impaired is preëminently diabetes mellitus. It stands alone by virtue of being the only condition in which the impairment of sugar combustion is specific; other processes, notably oxidations, remain normal. A variety of other conditions diminish the sugar-tolerance in non-specific manner; other bodily processes are disturbed as greatly as the sugar-economy. Among such

conditions are numerous forms of inanition (from starvation, cold, wasting disease, etc.) and intoxication (from drugs, acute and chronic disease, etc.). Thyroid intoxication, unless there is an accompanying disorder of the pancreas, probably disturbs the carbohydrate no more than the other metabolism. The exceedingly poor utilization of injected dextrose after parathyroidectomy was shown especially by Underhill and Saiki; but other disturbances of fatal nature are also present. In a third class may be considered all forms of hyperglycemia and glycosuria resulting from an abnormal production of sugar. In all these non-diabetic types, the actual power of combustion of dextrose is either normal or injured in non-specific manner, along with other bodily powers. But the agencies concerned give rise to an abnormal formation of sugar and an abnormally rapid destruction of glycogen. In this sense there is an alteration of the utilization of sugar; these forms of glycosuria are to be classified here, and not among the alterations of absorption or excretion. Even when not powerful enough to produce spontaneous glycosuria, all these agencies increase the tendency to alimentary glycosuria. Ingestion of sugar may be looked upon as one glycosuric agency; and with others, it obeys the law of *summation of effects of glycosuric agencies*. There are a few exceptions, but the general law is easily recognizable. The various glycosuric agencies will be discussed in later chapters, especially Chapter XII.

The influence of certain bodily conditions upon the power to utilize sugar must be considered before leaving this subject.

Pregnancy has been supposed to lower the sugar tolerance. Reichenstein (1) found glycosuria to result frequently from 100 g. dextrose in gravid women. Other literature will be found in the recent paper of Schirokauer (3), who proved that this dose of sugar produces no greater hyperglycemia in pregnant than in normal women.

Repeated doses of sugar are known to modify the tolerance slightly. Lepine [(1), p. 214] illustrates it by supposing that the same person ingests at the same time each day the same quantity of glucose, perhaps 100 g. For perhaps five days there may be no glycosuria. On the sixth day glycosuria may appear. Lepine advances an easy explanation; that the storage of sugar, either as glycogen or as fat, has its limits. The real reason why repeated doses of sugar have this curious effect upon the tolerance is unknown. It is as if some function became somewhat "tired."

Lepine's explanation is probably incorrect. Glycogen-richness does not diminish the tolerance for sugar. There is no evidence that any greater accumulation of glycogen is produced by preliminary sugar-feeding than by preliminary starch-feeding; but the starch-feeding will not lead to the results mentioned for the repeated doses of sugar. A dose of sugar alone will presumably form less glycogen than the same dose given with a meal of protein and starch; but glycosuria results in the former case more easily than in the latter. I have had oft-repeated occasion to observe that a well-fed, glycogen-rich animal assimilates as much dextrose subcutaneously as one that has fasted for any period from a day to a month. No distinction has been observable between the tolerance of sugar subcutaneously in dogs on meat-diet or on bread-diet.

CAT 48.

(Weight 2½ kilos).

Date	G. Dextrose Injected Subcut.	Urine	
		Quant. cc.	Sugar %
Oct. 21		90	-
" 22		120	-
" 23	4	112	-
" 24		85	-
" 25	6	100	-
" 26		107	-
" 27	8	110	-
" 28		93	-
" 29	10	115	-
" 30		110	-
" 31	11	105	0.45
Nov. 1		102	-
" 2	10	95	0.6
" 3		90	-
" 4	9	115	0.73
" 5		90	-
" 6	8	100	0.4
" 7		90	-
" 8	7	74	0.16
" 9		100	-
" 10	6	85	0.4
" 11		70	-
" 12	5	90	-

In giving daily subcutaneous injections of dextrose for a few days or weeks, I have seen no special variation of the tolerance. The same has been true of injections given two or three days apart. But curiously, it appears that the tolerance may be somewhat modified by injections every other day; at least, this happened in three cats, with no exceptions. Two of these cats were mentioned in Section 8. The most extreme example is shown in the accompanying table of Cat 48.

Pathological obesity is very commonly accompanied by a lowered assimilation-limit for sugar. This is not because the fat-laden body has less room to store additional sugar as fat, but probably because pathological obesity is a disease which in its nature is closely related to diabetes mellitus. Mere increase or decrease of the amount of body-fat of the healthy organism has no effect upon the sugar-tolerance one way or the other. Hofmeister [(1), p. 247] remarked that reckoning of sugar-dosage per kilo of body-weight is to some extent inaccurate, because the presence of fat alters the dosage but not the assimilation. He presents the case of a dog of 3400 g. weight, which assimilated fully 8 g., but not 10 g., of dextrose by mouth. When by fasting and insufficient diet the weight was brought down to 2420 g., the dog still assimilated his 8 g. of dextrose as completely as before.

I have observed repeatedly that variations in the body-weight have no effect upon the tolerance of dextrose given subcutaneously. The rule has held good not only for moderate but also for extreme variations. The point was of interest for two reasons. First, a very marked loading of the subcutaneous tissue with fat might possibly diminish the rapidity of absorption of the injected sugar. Second, Hofmeister's case in no way meets Lepine's suggestion. Hofmeister's dog had body-fat and was made to lose most of it. The present question, however, is whether an organism loaded and crammed with fat will be any less able to assimilate sugar. Reference may be made to Cat 46, a very vigorous female in the prime of life, but with lazy habits and unusually large appetite. When received, weighing 3030 g., she was noticeably fat. When caged on full diet, she had greater tendency than the average cat to grow excessively obese. She at one time reached the weight of 4420 g. As with all the animals, weights are those taken before feeding. The following is the record concerning sugar injections.

CAT 46.

Date.	Weight (grams).	Dextrose injected (grams).	Glycosuria.
Oct. 28	2650	10	0
Feb. 13	4145	15	Moderate.
Feb. 15	4060	17.5	Slight.
Feb. 17	4000	12.5	Slight to moderate.
Feb. 19	4020	10	Faint.
Feb. 23	3920	10	0
May 10	3430	10.24	Faint.

Thus, when decidedly plump at a weight of 2650 g. on October 28, the cat tolerated 10 g. dextrose subcutaneously without glycosuria. On May 10, when fat at a weight of 3430 g., the injection of 10.24 g. dextrose (about 3 g. per kilo) caused a glycosuria too faint to estimate quantitatively. During the period of February injections, when excessively obese at a weight of about 4 kilos, 10 g. dextrose caused a faint trace of glycosuria (influenced by the previous injections ?); 9 g. dextrose caused no glycosuria; repetition of the 10-gram dose then caused no glycosuria. Neither was the tolerance raised in proportion to the weight, for injection of 12½ g. produced well-marked glycosuria.

The conclusion is that variation in the fat-content of the normal organism does not alter the assimilation-limits for sugar.

Inanition, however, as already mentioned, must be sharply set apart from simple fluctuations of weight. Hofmeister (1) correctly drew this distinction; and he devoted an entire paper (2) to the hunger-glycosuria of dogs, which is an inanition-phenomenon sometimes sufficiently marked to occasion glycosuria after the ingestion of starch. Doyon and Dufourt arrived at results which are not really at variance with Hofmeister's. Their test of assimilation was the proportion of intravenously injected dextrose which the animal retained. They found no important difference produced in dogs by fasting as long as three weeks. The results, though accurate, are easily explainable. For one thing, strong dogs may come through a three-weeks fast with excellent strength. Again, the authors always figured their doses per kilo of body-weight, which is a good method; but yet Hofmeister showed how far a dog's weight may be reduced without reducing his tolerance. The actual conditions in the experiments of Doyon and Dufourt were, that after three weeks they were giving their dog about two-thirds the original quantity of sugar in grams, and the dog was excreting about the same proportion of this dose as of the original dose.

Dogs reduced to actual inanition have a very low dextrose tolerance, as Hofmeister found, and as the experiments in Chapter XIII show. Inanition lowers the tolerance of cats less than of dogs; there is no "hunger-glycosuria" of cats. In the numerous injections in fasting animals described in Chapter IV, it may be noticed that the same pro-kilo dosage is assimilated with the same efficiency almost up to death. The case of Cat 26 was an interesting illustration that chronic malnutrition and weakness may accom-

plish what direct starvation cannot. This cat was received in such a weakened condition that her survival was in question during several days. After two weeks under favorable conditions in the laboratory, a subcutaneous injection of 6 g. dextrose on September 3 caused decided glycosuria. By the end of October she had attained her normal tolerance, about 11 g. dextrose. The condition is somewhat suggestive of "vagabond" glycosuria.

The assimilation of any sugar is modified when another assimilable sugar is given simultaneously by the same or a different channel. Rosenberger (p. 67) refers to Worm-Müller as having found that men tolerate the addition of levulose to a maximum dose of dextrose better than the addition of dextrose; also to Brocard as having observed that less galactose is excreted when given with dextrose than when given alone. Rosenfeld (7) gave a dog 8 g. dextrose per kilo and the same quantity of levulose, both by mouth. He excreted 1 g. levulose and 2 g. dextrose. Another dog received the levulose by mouth and the dextrose intravenously. He excreted 20 g. dextrose and 18 g. levulose. The respiration experiments of Johansson are interpreted to mean that different sugars may be disposed of differently in the body.

Concerning (III). — The relative permeability of the kidneys for sugar is a factor, sometimes an important factor, in determining the presence or absence of glycosuria under a wide variety of conditions. The renal factor, like the other factors governing glycosuria, may produce effects in either direction; either toward causing glycosuria, or toward preventing it. Furthermore, while pathological conditions of the kidney are important, the variations noted are often seen when the kidney seems normal in all other respects. The extent to which the blood-sugar may be reduced and still permit glycosuria, is very limited as compared with the remarkable hyperglycemia which may sometimes exist without glycosuria.

Causes which Increase the Permeability of the Kidney for Sugar.

These are essentially two:

Diseases or injuries of the kidney.

Drugs or poisons affecting the kidney.

Phloridzin, frequently referred to as the type of a "renal" glycosuria, will be discussed in Chapter XV. The condition is not known to be an increased permeability of the kidney for the sugar of the blood. Renal glycosuria is considered in Chapter XII. The existence of a rare clinical form of glycosuria due to abnormal

renal permeability seems to be established. Experimental renal glycosuria has been produced by uranium salts and other renal poisons, by NaCl infusions, by nervous stimulation, by injections of organ extracts, by ligation of the ureters, and other renal injuries. Diuretic drugs facilitate glycosuria. The experimental caffein and diuretin glycosuria is accompanied by hyperglycemia, but the sugar excretion is increased by the diuresis. Von Noorden [(3), p. 530] was unable to observe any effect of diuretin upon alimentary glycosuria. But since then Lützow has shown that, in human patients, doses of caffein or diuretin which alone cause no glycosuria, and doses of sugar (50–100 g. dextrose) which alone cause no glycosuria, do produce glycosuria when given together. Pollak (1), using adrenalin and diuretin, has expressed the renal element in mathematical terms. Intravenous adrenalin injections are said regularly to cause hyperglycemia, but not glycosuria unless diuresis is provided for. In the rabbit, glycemia of 0.15–0.25 per cent gives rise to glycosuria provided there is diuresis. Without diuresis, for example in the hyperglycemia following laparotomy or simple intravenous injections of adrenalin, this percentage of blood-sugar causes no glycosuria. Blood-sugar above 0.25 per cent, as after subcutaneous injection of adrenalin, causes glycosuria whether there is diuresis or not.

Non-assimilable sugars, and salts such as NaCl, markedly lower the tolerance for dextrose, presumably by increasing the permeability of the kidney. Experimental examples are given in Chapter XV.

Causes which Diminish the Permeability of the Kidney for Sugar.

From the time of Claude Bernard till rather recently, the kidneys were looked upon essentially as a dam to a reservoir. The blood-sugar, like the water in the reservoir, could stand at a certain level without loss. If the level should rise, the excess must all flow out over the dam till the old height is restored. Pflüger [(1), p. 449] compares it to a glass running over. When the glass is full, all additional must flow off. Pavy [(1), p. 95] speaks of the "wonderful precision" of this mechanism; his views have been particularly extreme, because he has believed that all sugar which reaches the circulation as sugar is useless and must be excreted; only sugar which has first been synthesized into albumin or fat locally, before reaching the circulation, can be utilized in the body. It is now understood that the height of the

blood-sugar giving rise to glycosuria is very variable. As a general approximation, 0.2 per cent is regarded as the value which ordinarily represents the threshold of glycosuria in man. A few quotations may be given, illustrating especially the possibilities of hyperglycemia without glycosuria in the normal organism, before proceeding to the causes which raise the normal impermeability still higher.

Pavy and Godden (2), by slow and careful injections of dextrose intravenously in rabbits, could raise the blood-sugar to 0.2 per cent without glycosuria.

Gilbert and Baudouin (1) gave to human patients, 4 hours after the last meal, 150 g. dextrose made up with water to 400 cc. One hour later, blood-tests always showed increase of sugar; values from 0.107 per cent to 0.134 per cent in normal persons, and from 0.163 per cent to 0.246 per cent in cases of liver disease. There was no glycosuria in any case.

Frank finds that in alimentary and adrenalin glycosuria the blood-sugar must generally go above 0.2 per cent before glycosuria begins. In a rabbit he found even 0.3 per cent alimentary hyperglycemia without a trace of sugar in the urine. After glycosuria has once begun, it continues even after the blood-sugar has fallen almost to normal. The highest percentage in the urine comes an hour or so after the highest percentage in the blood. One hour after taking 200 g. dextrose, a patient had 0.212 per cent in blood and 0.515 per cent in urine. Two hours after the sugar-ingestion, the blood-sugar was 0.115 per cent and the urine contained 1.24 per cent.

Donath and Schlesinger, after oral administration of sugar in dogs, found that some animals showed glycosuria with normal blood-sugar (0.11 to 0.13 per cent), while others with no trace of glycosuria had a glycemia of 0.18 or 0.2 per cent.

The causes of increased impermeability of the kidneys for sugar may be imperfectly classified as follows:

Diseases and injuries of the kidney (nephritis, fever, etc.).
Drugs, especially renal poisons.
Action of sugar itself; also of salts.
Cachexia, extreme weakness, impaired circulation.
Nervous causes probably.
Unknown causes.

These causes may be considered in reverse order.

The unknown causes may include looser or firmer combinations of blood-sugar, by which various authors have tried to explain increased or decreased permeability of the kidney for sugar. In this connection, De Meyer has claimed to be able to render the excised kidney less permeable for sugar by adding pancreas-extract to the perfusion fluid. All sorts of hormones and other influences regulating the activity of the normal kidney may be included in this category of the unknown.

Nervous influences are hypothetical but probable.

Cachexia, extreme weakness, and impaired circulation may prevent excretion of sugar, because the function of the kidney suffers just as does that of all other organs. The assimilation of the diabetic is not increased thereby, but the sugar accumulates in the blood and tissues. The highest human blood-sugar ever recorded [Lepine (1), p. 454], of 1.06 per cent, was a terminal condition, with accompanying nephritis.

The action of sugar itself is generally held accountable for the diminished permeability of the diabetic kidney. It would not be surprising if the kidney should acquire habituation to the long-continued hyperglycemia. But Frank considers that a slow or gradual accommodation of the kidney cannot always be taken as the explanation; for he saw a case of light diabetes turn suddenly severe within 24 hours, and the sugar of the plasma rose at once to 0.56 per cent. Wilenko, using intravenous injections of concentrated salt and sugar solutions, found the effect to be first an increased and then a decreased permeability of the kidney for sugar.

Uranium and the other renal poisons, which at first increase the permeability of the kidney, at a later stage generally diminish it. Glutaric, tartaric and related acids act upon the kidney in such manner as to prevent or diminish glycosuria. A considerable list of substances [see Chapter XIX] may more or less completely suppress adrenalin glycosuria by an action upon the kidney; pancreas-extract is among them; the action is non-specific. Adrenalin itself [Pollak (1)] after repeated subcutaneous injections may continue to produce marked hyperglycemia, but glycosuria no longer appears, owing to some renal change.

There are numerous reports showing the extreme sugar-impermeability of the kidney which may be present in Bright's disease. For this reason, a nephritis complicating diabetes sometimes confuses the diagnosis, because of the slight or absent glycosuria,

while blood-examination may show hyperglycemia. Confusion is then possible with the hyperglycemia which sometimes accompanies nephritis, especially with uremia or apoplexy. Neubauer (2) reported a series of cases; in one nephritic patient, without diabetes or glycosuria, the blood-sugar was 0.21 per cent. Simple senility may render the kidney less permeable; Aldor observed that in the very old, alimentary glycosuria is much slower in beginning than in normal adults. In fever also there is frequently increased impermeability of the kidney, and hyperglycemia without glycosuria. Frank found blood-sugar of 0.202 per cent in a pneumonia; similar figures are contained in the tables of Liefmann and Stern below. Hollinger's paper is devoted to the subject. Experimentally, Wilenko (5) has found that repeated venesections, by injury of the kidneys through the blood, may diminish adrenalin glycosuria in rabbits, while hyperglycemia and diuresis are unchanged.

In uncomplicated diabetes, the relations between blood-sugar and urine-sugar are widely variable. Hyperglycemia with glycosuria is of course the rule. Frank's case is an extreme example; blood-sugar 0.5 per cent, glycosuria 8 per cent; total daily excretion 300 to 400 g. Gilbert and Baudouin (2) report a series of cases in which daily analyses showed parallelism between glycemia and glycosuria. Discrepancies between the two are more frequently reported in the literature. For example, Hesse and Mohr state that after complete extirpation of the pancreas in well-nourished dogs, blood-sugar may occasionally be far above the normal, without glycosuria. Falta (5) mentions cases along the lines of Liefmann and Stern. In one of them, with a daily sugar-excretion of 5 g., the blood-sugar was 0.36 per cent. On the twenty-third day after disappearance of glycosuria, the glycemia was still 0.123 per cent. Another more striking case, 9 days after cessation of glycosuria, had a blood-sugar of 0.21 per cent. Weiland (2) presents a number of blood-analyses illustrating the same point, and recommends such analyses as routine in diabetes, because of the unreliability of glycosuria as a sole guide. Neubauer (2) studied the hyperglycemia both of nephritis and of diabetes. The researches of Liefmann and Stern, published in 1906, were what really awakened general interest in this subject; and they remain classical. They proposed the terms "inner tolerance" and "outer tolerance" for sugar. The first means essentially the blood-sugar regulation and the ability of the tissues to use sugar. The second

means the permeability of the kidney for sugar. Two of their tables are here reproduced. The first table illustrates the incongruence between glycemia and glycosuria in diabetes. The effects of nephritis are evident; and those of the terminal uremic-diabetic coma furnish the most extreme examples.

	NAME	DURATION OF DIABETES	URINE	BLOOD	REMARKS
Diabetes doubtful or not present.	Ki.	0	0	0.105	
	Bu.	?	0	0.114	
Duration up to a year	Ro.	Known for 8 days	Trace	0.105	
	Ro.	" " 8 "	0.1	0.115	
	Sch.	" " 2 months	1.3	0.28	
	Gr.	1/2 year	2.0	0.25	
	Gr.	1/2 year	0	0.095	
	Co.	7 months	1.2	0.152	
	Co.	7 months	0	0.11	
	Co.	7 months	0	0.12	
	Co.	7 months	0.7	0.163	
	Kl.	1 year	0	0.152	
1-2 years	Ma.	1 1/2 years	0.7	0.17	
	La.	2 years	2.1	0.247	
	E.	2 years	5.1	0.268	
3 years	Kr.	3 years	Trace	0.134	
	Jo.	3 years	1.9	0.209	
4-5 years	Schl.	4-5 years	0	0.163	
	Schl.	4-5 years	0.97	0.2	
	Schw.	4-5 years	Trace	0.188	
	Schw.	4-5 years	1.05	0.204	
	Pr.	4-5 years	4.85	0.209	
10-15 years	St.	10 years	0	0.154	
	W.	15 years	Trace	0.224	
Diabetes and Albuminuria	Kn.	Few Days	0	0.143	1/8 0/00 Albumin
	Kn.	" "	0.26	0.152	
Diabetes and Nephritis	We.	Few Days	4.4	0.381	
	Ey.	4-5 years	2.4	0.286	
	Ey.	4-5 years	0	0.183	First Sugar-free specimen.
	Ey.	4-5 years	0	0.107	Sugar-free for a considerable time.
Brain-tumor with glycosuria	Se.	?	?	0.237	
Coma, diabetic and uremic	H.	?	3.9	0.44	
	G.	?	3.89	0.573	
	Schl.	2 years	3.1	0.53	
	Schl.	2 years	Trace	1.01	
	Kr.	?	1.4	0.85	Uremia
Alimentary glycosuria	Ka.	---	0.2	0.218	
	Ma.	---	1.0	0.147	
	Ko.	---	2.7	0.126	
	Hol.	---	---	0.0812	Normal
	Hol.	---	---	0.069	100 g. glucose
	Hol.	---	0.52	0.098	200 g. glucose

The following table deals not with diabetes, but with croupous pneumonia patients. It illustrates the hyperglycemia that is common in fever, and the ease with which alimentary hyperglycemia but not necessarily glycosuria may be produced. Since sugar is not a harmful substance, there is no ground for thinking that the patient here with 0.281 per cent of blood-sugar suffered any injury from this excess.

NAME	URINE		BLOOD	REMARKS
	ALB.	SUGAR		
1. M. . .	?	0	0.098	
2. A. . .	0	0	0.105	
	0	0	0.17	1 hour after ingestion of 200 g. glucose.
3. R. . .	+	0	0.136	
	+	0	0.281	1 hour after ingestion of 100 g. glucose.
4. Pr. . .	0	0	0.155	

Further figures in this connection are found in the work of Tachau, mentioned in Section 15 of this chapter.

11. Intravenous Injections of Dextrose.

Experiments with intravenous injections of sugar are legion; and the different purposes for which they have been performed are almost equally numerous. Only a few examples will be presented, in order to give a general idea of the behavior of sugars introduced by this route.

Lamy and Mayer, Arrous, and others [see Chapter VI] frequently injected enormous doses, either in dogs or in rabbits, and the injury to the animals was surprisingly small, everything considered. Harley tied the ureters in dogs, and then injected 10 to 12 g. dextrose per kilo intravenously, at the rate of 2 or 3 g. every 2 minutes, the total injection lasting about an hour. Larger dogs bore 12 g. per kilo well; small dogs were killed by anything above 10 g. per kilo. The hyperglycemia disappeared within a few hours.

Brasol investigated how the blood frees itself of the excess of intravenously injected sugar. The sugar quickly disappears from the circulation as a result of osmosis and transformation. It diffuses into the corpuscles, which retain it longer than the plasma. Pavy (3) performed intravenous injections of various sugars, and extensive analyses of the blood and urine at different intervals. He found that injected dextrose quickly undergoes change in the circulation, so that copper reduction in blood specimens is much

greater after inversion than before. No such change occurs with galactose, and it is doubtful with levulose. Verzár (2), from a study of the respiratory quotient, found that the intravenously injected sugar is burned.

Injected sugars produce various bodily effects, some known, many doubtless unknown. Large doses always cause albuminuria. Smaller doses can be injected, even in the rabbit, without albuminuria. The findings of Wilenko (3), that concentrated salt or sugar solutions first increase and later diminish the permeability of the kidney, have been mentioned. He attributes the effects to the osmotic properties. Postmortem, animals dead of excessive sugar injections may show a few parenchymatous changes attributable to osmosis; but nobody has ever reported any pathological lesion characteristic of sugar. Calabresi has confirmed the statement of Cavazzani and Ferrari, that intravenous dextrose injections during life delay the postmortem formation of sugar in the liver. Injections lasting ten minutes seem to be as effective in this regard as longer injections.

All writers are agreed that, irrespective of the dose, more sugar is always retained than is excreted. A number have undertaken to establish a standard of intravenous tolerance, that is, the threshold dose that can be assimilated without glycosuria. Lepine [(1), p. 236] discusses the intravenous tolerance.

Gilbert and Carnot (1) claimed a fixed relation between injection and excretion, varying somewhat with the individual rabbit, but independent of dosage. Their doses ranged from 3.6 to 23 g. Their figures for the normal show the constant $\frac{\text{excretion}}{\text{injection}}$ = approximately $\frac{44}{100}$. Also (2), they tried the effects of various drugs upon this formula. Phloridzin increases the excretion, making the ratio stand $\frac{56.3}{100}$. Salts of manganese, by renal injury, diminish excretion and bring the ratio down to $\frac{13}{100}$ or $\frac{12}{100}$.

A standard such as the above may perhaps be approximated under fixed conditions; but variations will necessarily occur with differences in operative methods, rate of injection, concentration of solution, renal injury, etc.

McGuigan (3) used 0.5 per cent solutions of sugars in water, to avoid effects of NaCl. For dextrose, injected into the jugular vein of rabbits at the rate of 1 cc. per minute, he found that 40 cc. must be administered before glycosuria results. An effect of water upon the rabbit's kidney is here a possibility.

Pavy [(2), pp. 188–90] found hyperglycemia and glycosuria after intravenous injection of 0.5 to 1 g. per kilo in rabbits. These results are confused by the fact that he used "honey solution," a mixture of dextrose and levulose. Pavy and Godden (2) showed the opposite effects of quick and slow dextrose injections. By the slow method they could administer considerable sugar without glycosuria, even though the glycemia might reach 0.2 per cent.

Blumenthal made the most notable attempt to standardize conditions for the determination of the assimilation-limit of sugar intravenously. He chose this method as giving the purest results, free from all the possible irregularities of absorption that may attend oral or other tests. He found that the amount which causes glycosuria varies between 1.8 g. and 2.8 g. per rabbit (about 0.8 g. per kilo), in injections lasting 1 to 10 minutes. The exact number of minutes within these limits made no great difference. The figure found for a given rabbit is constant for future injections to within 0.1 g. Increased quantity of liquid by dilution increases glycosuria a trifle. It is possible to inject the saturation-quantity rapidly without glycosuria; but after that, a very small addition, even $\frac{1}{50}$ to $\frac{1}{80}$ of the saturation quantity, suffices for glycosuria. The saturation limits of dextrose and levulose are almost equal; for galactose it is much less; for saccharose and lactose it is very small.

Comessatti (1) used the Blumenthal method for demonstrating the increased sugar-assimilation in rabbits in consequence of muscular work. For normal rabbits weighing $2\frac{1}{2}$ to 3 kilos, the tolerance was between 2 and $2\frac{1}{2}$ g. dextrose. By running in a treadmill the tolerance was raised by about 20 per cent. Tolerance of levulose was also raised; and that of galactose a little.

McCurdy used the Blumenthal method, and demonstrated by it an increased assimilation limit for dextrose in thyroidectomized dogs. As compared with Blumenthal's figure of 0.8 g. per kilo for saturation in rabbits, McCurdy places the limit in dogs at 0.4 g. per kilo.

Carlson and Martin, on the other hand, have found the tolerance of normal dogs by this method to vary between 0.9 and 1.5 g. per kilo.

Doyon and Dufourt used large intravenous injections for judging the modifications of tolerance produced by starvation, alcohol, and icterus.

The intravenous method has also been used in human beings. Tuckett performed interesting injections of dextrose into his own veins, and found his tolerance not altered by different diets or by fasting. Biedl and Kraus gave patients intravenous injections of 200–300 cc. of 10% dextrose solution. Neither glycosuria nor polyuria was determinable in the 24-hour urine. By catheterization of the ureters, the injections were found to cause a temporary increase of urine, with glycosuria of 0.5 to 2 per cent. Kausch (3) and his assistant Berendes have recently advocated the use of intravenous injections of dextrose for their stimulating and nutritive effects in human patients, in a considerable variety of dangerous medical and surgical conditions. [See Chapter IV.] Here the limits of tolerance are of interest. The solutions were 2 to 10 per cent, generally 5 per cent. Intravenous injections of 1 to 2 litres were given slowly without ill effect, and glycosuria was absent or insignificant. One woman, with puerperal sepsis and temperature above 40 degrees, for six days received up to 2900 cc. daily, with excretion varying only from 0.2 g. to 3 g. The speed of injection is an important factor.

Concerning the general subject of intravenous injections, the following closing remarks are in order. Such injections are unquestionably well borne, especially if given slowly. Albuminuria is a little more common by the intravenous than by the subcutaneous method. But what was found by some authors in studying the toxicity of salts, applies also to injections of sugar even in large amounts, viz.: that the temperature elevation is apt to be lower and less prolonged by the intravenous than by the subcutaneous method. Either method with large doses may cause diarrhea. The behavior of the animal indicates less prostration by the intravenous than by the subcutaneous route.

As a test of sugar-tolerance, the intravenous method has at least one obvious advantage, viz.: the accurate introduction of a definite dose within a definite time, independent of all delay or irregularity of absorption. There are attendant disadvantages. According to Wilenko, large doses alter renal permeability. The Blumenthal test, the one most commonly used, consists in the sudden introduction into the circulation of that small quantity of sugar which can be held by the blood (and tissue fluids) without overflowing the kidney. Accordingly, two factors govern it; the permeability of the kidney, and the binding power of the blood and tissues. The former, therefore, probably acquires greater

importance than it possesses in the case of sugar given by mouth, subcutaneously, or intraperitoneally. The second factor, the power of the blood and tissues to bind sugar, may or may not run parallel with the ability of the tissues to utilize sugar, and the latter is what in most cases we actually desire to test. Comparison of the results of this and other methods may be interesting. As will be more fully detailed in the next chapter, for galactose the intravenous, subcutaneous, and oral methods agree in showing a relatively low tolerance; for lactose and saccharose the comparative figures yielded by the Blumenthal method are too high; for levulose the saturation-limit shown by the Blumenthal test is practically equal to that of dextrose, the oral tolerance is lower even though the liver presumably stops most of the levulose, and the subcutaneous test reveals the true facts, viz.: that the assimilation of levulose by the tissues is far inferior to that of dextrose. Concerning dextrose, which is the present topic, there is little direct information. The reliability of the method as a standard of comparison is doubtful, in view of the widely discrepant findings of McCurdy on the one hand and Carlson and Martin on the other; such differences are not encountered with the subcutaneous method. The experience with the other sugars indicates that the amount of sugar which can be held by the fluids without overflowing the kidney is not necessarily a measure of the power of the tissues to utilize sugar. The *rate of utilization* is the essential thing to be tested; not the quantity of sugar which may perhaps circulate and recirculate in the blood without overflowing the kidney, but the speed with which the tissues can withdraw the sugar from the blood. It seems doubtful if the diminished tolerance regularly shown in partially depancreatized dogs by the subcutaneous method can be demonstrated by the Blumenthal method. This method may yield results interesting for comparison with those of other methods; but its apparent exactness is probably fallacious, and it cannot be accepted without further demonstration as a test of the power of the tissues to utilize sugar.

12. Subcutaneous Injections of Dextrose.

The investigators who have used dextrose subcutaneously, and the purposes for which they have used it, have been sufficiently treated in the foregoing sections. In general, subcutaneous sugar-injections are well borne. The alarming pictures described by Kossa for birds are not seen in mammals. Among the protocols

of my dogs will be found a number of injections of different sugars in dosage of 10, 12 or 15 g. per kilo. Heilner gave rabbits 10 g. per kilo subcutaneously, and some of Fichtenmayer's huge injections figured as high as 35 g. per kilo; his rabbits evidently were unusually strong. After large doses, diarrhea is common. Albuminuria occurs somewhat less readily, and is more dependent upon the concentration of solution; doses up to 10 g. per kilo seldom produce it in dogs or cats with isotonic or double-isotonic solution. Elevation of temperature is the rule, though there are exceptions. The rabbit may react with very high temperatures, above 105° F. In other animals, especially dogs and cats, hyperpyrexia never occurs. The commonest evening temperature after a morning or noon injection is between 102° and 103° F. Anything above 103 degrees is suspicious. If it goes above 104 degrees, look for the abscess. By the next morning the temperature is ordinarily back to normal or practically so. If it remains up, infection is probable.

In view of the possible diagnostic or therapeutic uses of subcutaneous injections of dextrose, the possible by-effects of the injections in man are of interest. Leube witnessed intense inflammation and even necrosis of the skin; but his solutions were concentrated. F. Voit gave considerable quantities of 10 per cent solution, generally under the skin of the thigh, with perfect impunity. J. Müller adopted Voit's procedure in a test upon himself; there was no discomfort for 12 hours; then the limb was swollen and painful for several days. It is perhaps better to use the isotonic 5 per cent solution; yet Müller's account reads somewhat like an accidental slight infection. Schmidt and Meyer say that 10 per cent injections may be painful in human patients. Kausch and Berendes, the latest in this field, have used the 5 per cent solution frequently, and say it hurts nobody; if it is given in one thigh, and plain saline in the other, the patient cannot distinguish between them. But to avoid even such discomfort and inconvenience as proceed from a saline hypodermoclysis, they prefer the intravenous administration.

Absorption of the injections is a point to be considered. Clinicians think of subcutaneous absorption as rapid, but the testimony concerning dextrose is that it is fairly slow. Heilner (1) is the only person who has investigated the question accurately. When one of his rabbits received 16 g. dextrose (5 g. per kilo) in 10 per cent solution on one side of the body in the morning, and the same

dose on the other side in the evening, and was killed the next morning, the tissue from the region of the first injection was found to be negative for sugar, but the slight œdema-fluid remaining at the site of the second injection gave a positive reduction test. When single injections of about 32 g. were given (10 g. per kilo) in rabbits which had fasted 4 days, and the animals killed at the end of 24 hours and the entire body analyzed for dextrose, the quantity found in the entire body was about 15 per cent of the total quantity injected 24 hours previously. This of course does not mean that the sugar was all lying unabsorbed at the site of injection; Heilner's purpose here was merely to learn how much of the amount injected had been burned or transformed. The local œdema which Heilner notes after his 10 per cent injections is more marked after stronger concentrations. But even with a $7\frac{1}{2}$ per cent solution, Gumprecht found at autopsy a certain amount of clear fluid about the field of injection. This was sometimes merely unabsorbed sugar-solution, but at other times it was sugar-free. He concluded that the sugar is absorbed more quickly than the tissue-fluid accumulated by its osmotic properties.

Heilner's work determined essentially how long the process of complete absorption may require. It should be borne in mind that sugar is absorbed more rapidly as it is more concentrated. The absorption at first is probably rapid. Blood-sugar analyses would decide the question, but none seem to have been made. The rapid initial absorption is evidenced by the quick flooding of the body and appearance of glycosuria. Glycosuria may appear in half an hour after injection, or less. In a diabetic dog, I have seen the beginning of excretion within fifteen minutes after injection. When an injection is given in the middle of the forenoon, in quantity sufficient only for slight glycosuria, the latter may have disappeared by the middle of the afternoon, or there may be vestiges in the 5 p.m. urine. It is almost or quite impossible to inject enough dextrose to make the glycosuria continue past the first 24-hour period.

What becomes of the subcutaneously introduced dextrose has been answered by a number of investigators (Sachs, Gumprecht, Lusk, Heilner and others). As it is not excreted, it must be consumed somehow. To some extent it forms glycogen both in liver and muscles. Respiration experiments prove that much of the sugar is burned. With the exception of such shreds of evidence

as the excretion of glycuronic or oxalic acid, we have no knowledge whether the disposal of the abnormal mass of sugar is by normal or abnormal processes. An abnormal process under such conditions would not be surprising.

Clinically, the subcutaneous test of assimilation is not likely to be used, unless for some special reason. For animals, it is the best of all methods, and should be adopted as the standard procedure. It is harmless, highly convenient, and accurate. Some of the confusion and mistakes in regard to carbohydrate metabolism have arisen from the imperfections of the tests employed. The accuracy of the subcutaneous method permits easy demonstration of the disturbance of dextrose-tolerance which invariably results when any large portion of the pancreas is removed. The following points in the use of the test may be noted.

First, absorption seems to be uniform. Except in extreme prostration with impaired circulation, there have been no exceptions to this rule; and even in these cases, absorption is perhaps better than after oral administration.

Second, the portion of the body-surface of an animal chosen for injection seems to be without influence. Doubtless, an injection in the paw or tail might be less rapidly absorbed; but for the body in general, the results are everywhere the same.

Third, the concentration of solution is practically or absolutely without effect upon the tolerance. Perhaps the increased osmosis in strong solutions balances the wider distribution in dilute solutions.

13. Intraperitoneal Injections of Dextrose.

Intraperitoneal injections are analogous to the subcutaneous, with a somewhat lower tolerance due presumably to more rapid absorption. Infection, unusual pain, or other complications are absent with reasonable concentrations of solution. Accurate tests of the tolerance seem not to have been made.

Nobecourt and Bigart observed the effect of intraperitoneal injections of dextrose upon the excretion of urea and chlorides in rabbits. Doses sufficient or insufficient for glycosuria caused increased output of urea. Large doses increase, small doses do not increase, the excretion of chlorides. Schmidt and Meyer have done the most complete work on the subject. Dogs assimilated the full doses injected. A "medium-sized" sheep-dog received 500 cc. of 10 per cent dextrose into the peritoneum without glyco-

suria. In a human case, intraperitoneal injection of 5 per cent dextrose solution was painless, but autopsy showed well-marked irritation of the peritoneum. The authors suggest that human tissues are apparently more sensitive to sugar than those of lower animals. My experiences with intraperitoneal injections have been few and incidental. The case of Dog 28, with simultaneous subcutaneous and intraperitoneal injection of dextrose, was mentioned in connection with intestinal excretion of sugar. In a few instances, some idea of the intraperitoneal tolerance was obtained.

Dog 34 (weight 6350 g.) on April 18 received 203.2 cc. 25 per cent dextrose solution into the peritoneum (8 g. per kilo). The injection was given slowly through a needle, requiring about 15 minutes. Immediately after injection urine was passed, containing 0.5 per cent dextrose. Half an hour later the glycosuria was 16.6 per cent and the blood-sugar 0.43 per cent. An hour after injection the glycosuria was 10.4 per cent. As the total urine passed was 2 cc., the sugar-excretion was insignificant. There was great prostration, which mostly disappeared by the next day. The feebleness of circulation during the period of prostration was such that gangrene resulted in the leg in which the femoral artery had been cannulated for collecting blood; and the dog was therefore killed three days after injection. The experiment indicates that the tolerance is much less and the prostration much greater with intraperitoneal than with subcutaneous injection.

Cat 46 received intraperitoneal injections of dextrose on November 7 and 8, in 10 per cent solution. On November 7 the dose was 1 g., on November 8 it was 5 g. The latter dose represented about $1\frac{1}{2}$ g. per kilo. There was no glycosuria. The subcutaneous tolerance of this cat was about 3 g. per kilo. The intraperitoneal tolerance was therefore more than half the subcutaneous tolerance.

Rat 2 received on December 5 an intraperitoneal injection of 3 cc. 10 per cent dextrose, and on December 22 a subcutaneous injection of 3 cc. 40 per cent dextrose. There was a similar slight glycosuria in each case. The intraperitoneal was therefore approximately one-fourth the subcutaneous tolerance. The relations in Rat 1A, a partially depancreatized animal, on the same dates were similar.

14. Rectal Administration of Carbohydrates.

As I have had no experience with rectal injections, and shall therefore not return to this phase of the subject, the rectal administration of various sugars and other carbohydrates will be treated here under one heading.

Voit and Bauer are credited with being the first to institute systematic researches concerning the value of nutrient enemas and the absorptive capabilities of the large intestine. They used no carbohydrates except a few starch enemas.

Eichhorst made a careful investigation of the absorption of albuminous substances by the large intestine. Two incidental observations attracted his notice; first, sugar in the urine after rectal infusion of milk; second, sugar in the urine after rectal infusion of honey. Present knowledge apparently justifies the conclusion that the sugar present in the first instance was lactose, and in the second instance was levulose. Schoenborn in Leube's clinic was able to give patients considerable quantities of dextrose by rectum, and to prove that they absorbed all or most of it. They were required to retain the enemas generally for one hour, sometimes for several. After longer retention, absorption was sometimes complete; but in all cases by far the greater portion of the injected sugar was absorbed. The concentrations used were generally about 12 to 16 per cent. The largest quantity administered was 174 g., in two cases; after one hour, the rectal washings contained 42.4 g. dextrose in one case and 30 g. dextrose in the other. Such a dose ordinarily caused slight diarrhea; and the author thinks 150 to 170 g. is the maximum dosage to be recommended. Glycosuria never resulted, even though the author tried giving the sugar in an unusually large quantity of very dilute solution, in the attempt to obtain absorption through the lymphatics and thus test the views of alimentary glycosuria attributed to Ginsberg. But a positive result was claimed when the absorption of the sugar was artificially limited to the lower 10 cm. of the rectum, in order that it might be absorbed into the middle hemorrhoidal vessels, and thus flow directly into the systemic circulation instead of into the tributaries of the portal system.

Reach (1) published experiments by improved methods, contradicting the earlier claims. He studied the respiratory quotient. Enemas of 60 g. sugar or dextrin in 120 to 200 cc. water, or of 100 g. starch in 300 cc. water, failed to influence the gaseous exchange

perceptibly, though the same quantities by mouth show a well-marked effect upon the quotient. Glycosuria or dextrinuria never resulted. He concluded that some sugar is probably absorbed, but only a small quantity compared with the same dose by mouth. Absorption of sugar is slow, of dextrin slower, and of starch very slow and unsatisfactory. Dextrin makes one of the best enemas, for its ultimate absorption compares fairly well with that of sugar, and it irritates the rectum less. The infant-foods consisting largely of dextrin should make satisfactory enemas.

Arnheim imitated Schoenborn's procedure in a diabetic patient. He shut off the upper bowel by means of a tampon, so as to permit absorption only from the lowest portion of the rectum. The sugar thus given was nearly all assimilated, and reappeared neither in the feces nor in the urine. The author questioned whether it was utilized because of avoidance of the liver, or because of slow absorption.

Halasz (3) obtained results opposite to those of Reach. His work was with sugar-enemas in human patients and dogs. In some dogs the lower bowel was ligated off, to prove conclusively that absorption occurred only from it. The respiratory quotient proved that under these conditions the sugar was rapidly absorbed and utilized. Disaccharides are said to be split, by invertin of the bowel or by bacterial action. But the actual destruction of sugar by bacteria is shown, by incubation experiments with feces in vitro, to be negligible; probably between 0.5 and 1 per cent. Large quantities were absorbed under the conditions described, not passing through the liver and yet not causing glycosuria. The author thinks the slowness of the absorption accounts for this result.

Balint has recently contributed to the question as to the value of sugar-enemas in diabetes. That sugar by this route may be utilized by diabetics is well known. The author believes that the explanation lies in the slow absorption, not in the avoidance of the portal circulation. He finds that these enemas do not combat acidosis as does the same quantity of sugar by mouth. Patients who on a definite quantity of sugar by mouth were showing little or no acidosis exhibited a marked increase of acidosis when the mouth-feeding was stopped and the identical quantity of sugar was given by rectum. But by the institution of one or two fast-days, during which the patient receives prolonged rectal infusion of sugar drop by drop, the author claims that glycosuria disappears and there is no acidosis.

Apparently rectal administration of sugar is the one method by which glycosuria is impossible under normal conditions. It is conceivable that it might be obtained experimentally by introducing a large quantity in an animal and then ligating the bowel. But in man, Schoenborn's 174 g. dextrose in a litre of water is probably the upper limit. It causes no glycosuria. Sugar solutions are irritating at best; and if the quantity or concentration is increased beyond the figures specified, the attempt is ended by diarrhea.

15. Oral Administration of Dextrose.

The oral administration of dextrose is the customary and most convenient test of the power of sugar assimilation in human beings. As previously mentioned, 100 g. is the standard quantity, though most normal persons can completely assimilate 200 g. or even more. These amounts sometimes produce slight disturbances, and the excessive doses occasionally used in animal experiments may endanger life. Vomiting and diarrhea are the signs of osmotic irritation of the alimentary tract. That osmosis has a share in the fatal outcome, at least in small animals, is shown by Mitchell's cataract experiments, in which frogs died under the enormous doses if deprived of water, but lived if allowed to lie in water. Hildebrandt's rabbits survived the oral administration of 30 g. dextrose per kilo when on the ordinary "alkaline" diet, but died (unless they received chalk) if kept on an "acid" diet of oats. He considered that death was due to oxalate poisoning.

Differences in the rate of absorption affect the results of this test markedly, and a uniform method is desirable. Von Noorden gives the sugar fasting, and finds the normal assimilation 150–180 g. To give the sugar in the morning before breakfast is a prevalent clinical method. Gilbert and Baudouin gave 150 g. dextrose made up with water to 400 cc., 4 hours after the last meal. Standard concentrations of this nature are of some importance, for, contrary to what is true with subcutaneous administration, dilution increases the tendency to glycosuria. Naunyn (p. 37) opposes using the test while fasting, because of the alleged occasional occurrence of atypical positive results. He recommends the following procedure. The patient has a breakfast of 80–100 g. bread, and up to 250 cc. of coffee with milk. Two hours later he receives 100 g. dextrose. If glycosuria occurs to a quantitatively determinable degree, a lowering of the power of sugar assimilation is demonstrated. Mere traces in the urine are

without significance. The most accurate method is probably that of Schlesinger, which consists in giving repeated doses, and determining the limit as that quantity beyond which an increase of dose produces an increase of excretion.

The test for alimentary glycosuria is used especially in cases of suspected diabetes. Other clinical conditions sometimes accompanied by a lowering of dextrose assimilation are nervous disorders, liver diseases, acute febrile infections, hyperthyroidism, alcoholic and other intoxications, etc. Alimentary glycosuria is not a test of the hepatic function [see Weintrand (2)]; levulose was introduced for this purpose by Strauss. An increase above the normal sugar-tolerance may be found in conditions such as hypothyroidism, adrenal deficiency, and some pituitary disorders; it is not yet clearly demonstrated whether in these conditions, in which the other bodily functions are generally sluggish, there is an actual increase in the rate of utilization of dextrose, or whether the apparent increase of tolerance represents merely a delayed absorption of the sugar and an impaired permeability of the kidney. At the present time, alimentary glycosuria is not likely to be confused with the excretion of other reducing substances in alkaptonuria, levulosuria, and the lactosuria of young infants and of pregnant or lactating women, though in the latter the ingestion of dextrose may increase the excretion of lactose. Concerning the time-limits of alimentary glycosuria, von Noorden [(1), p. 21] states that it begins generally $\frac{3}{4}$ to 1 hour after a large dose of sugar, and lasts 1 to 3 hours. The total excretion is seldom over 2 per cent, never over 5 per cent, of the amount ingested.

Under various unknown and known conditions, the most marked of which is Bright's disease, the test may be obscured by impermeability of the kidney. Even diabetes, when complicated by nephritis, may react negatively to the test of alimentary glycosuria, the sugar merely heaping up in the blood. For this reason, examination of the blood is most important to accompany or replace examination of the urine; and the most recent studies concerning lowered assimilation of sugar are based not upon alimentary glycosuria but upon alimentary hyperglycemia. Mention has already been made of the findings of Donath and Schlesinger with alimentary tests in dogs [in some animals glycosuria with nearly normal blood-sugar (0.11–0.13 per cent), in other animals hyperglycemia (0.18–0.2 per cent) without glycosuria],

also of Gilbert and Baudouin (1) [in normal human subjects, one hour after 150 g. glucose, blood-sugar values of 0.107–0.134 per cent, and in patients with liver-disease 0.163–0.246 per cent; no glycosuria in any case]. The incongruous relations between blood-sugar and urine-sugar have been shown by Tachau (1), from whose tables the following table is condensed. His procedure was to test the blood-sugar fasting and 1 hour after 100 g. dextrose by mouth. In a normal person the dose increases the blood-sugar very little. In diabetes the fasting percentage is usually high, and is markedly increased by dextrose or other carbohydrate. In fever the fasting value is generally high, but it depends on severity of intoxication rather than on height of temperature; alimentary hyperglycemia is the rule, but even when pronounced, often leads to no glycosuria. Cases of nephritis without uremia showed no hyperglycemia either fasting or after dextrose. In cases of liver-trouble and icterus, alimentary hyperglycemia is common. The figures given below generally represent maximum and minimum values found in a series of cases in the author's complete tables.

Condition	Blood-Sugar		Glycosuria
	Fasting	After 100g. Dextrose	
Normal	0.085-0.086%	0.06-0.107%	0
Diabetes	0.11 -0.169%	0.207-0.225%	0.3-0.4%
Lead-poisoning (with glycosuria)	0.097%	0.149%	0.1%
Four other cases of lead-poisoning	0.105%	0.121-0.256%	Neg.in 3 out of 4
Various fevers	0.085-0.11%	0.125-0.2%	0
Chronic Nephritis	0.091-0.104%	0.111-0.216%	0

Tachau explains on a reasonable basis why at some periods after ingestion of sugar the blood analysis may reveal a hypoglycemia. His hypothesis is that during the hyperglycemia all the peripheral depots become loaded with sugar and glycogen. In this condition, the need of supplies of sugar from the liver is diminished, hence the diminished transport of sugar in the blood. Tachau closes by recommending the blood-test as a more accurate index of sugar-tolerance than the urinary examination.

Reicher and Stein, with a colorimetric method which showed 0.09–0.15 per cent blood-carbohydrate as the normal limits, found that within an hour after ingestion of 100 g. dextrose these values rise to 0.2–0.25 per cent, then rapidly sink. The observation is interesting as indicating that other carbohydrate substances besides dextrose are increased in the blood after ingestion of dextrose. Agreement concerning the occurrence of increased blood-sugar in normal persons after 100 g. dextrose is not yet perfect. Several have failed to find it. Hegler has recently missed it in normal subjects, but has found it well-marked in alimentary glycosuria, pneumonia (existing hyperglycemia increased), hepatic cirrhosis, and chronic alcoholism. Possibly "normal" subjects vary (it is said that alimentary glycosuria is easier to produce in persons of the upper than in those of the lower classes). Positive results here outweigh negative; and it must be concluded that increase of the blood-sugar after 100 g. dextrose may occur in normal persons, and to still greater extent in a considerable number of patients who show no glycosuria.

The above conclusions concerning human patients are confirmed by the recent animal experiments of Fisher and Wishart. After feeding 50 g. dextrose to dogs weighing 8–9 kilos, they found blood-sugar values as follows:

	Per cent
After 1 hour	0.16
After 1 hour	0.13
After 2 hours	0.10
After 2 hours	0.11
After 3 hours	0.11
After 4 hours	0.11

16. Mechanism of Alimentary Hyperglycemia and Glycosuria.

Until recently, it was a prevalent opinion that the liver is necessary for stopping and retaining the sugar absorbed from the intestine; and that the hyperglycemia and glycosuria which follow large doses of sugar result from absorption by the lymphatics, which carry the sugar through the thoracic duct into the systemic circulation with avoidance of the liver. Though the incorrectness of this view is now generally recognized, a brief mention of some of the evidence on both sides may be worth while.

Claude Bernard established the doctrine that absorbed sugar must be stopped by the liver in order to prevent glycosuria. As one of the proofs of his position, he obliterated the portal vein in

dogs, and in consequence observed glycosuria on a diet of potatoes [Bernard (3), pp. 316, 334, 339].

Bock and Hoffmann found that after exclusion of the liver in rabbits, and simultaneous ligation of the lymphatics from the intestine, the sugar disappeared from the blood in 45 minutes; but without ligation of the lymphatics the disappearance required 80 minutes. They concluded that absorption of sugar by the lymphatics is not a negligible factor, at least when the portal vein is tied.

Von Mering demonstrated that the chyle contains equal amounts of sugar in dogs fed on meat or on large quantities of starch and sugar.

Heidenhain (1) suggested the anatomical relations in favor of absorption chiefly through the blood-vessels, which occupy the periphery of the villi; but if these were overflowed by excessive quantities, he considered that some sugar might reach the lymphatics. He showed that water given in sufficiently large amounts may be to a slight extent absorbed through the lymphatics. His pupil Ginsberg then took up the question.

Ginsberg used rabbits and dogs in which Heidenhain had established thoracic-duct fistulas, and made sugar-analyses of the blood and lymph before and after the giving of sugar by stomach-tube. The chyle of normal rabbits was found to contain 0.23–0.25 per cent sugar. After giving 5 to 25 g. dextrose by stomach tube (2 to $7\frac{1}{2}$ g. per kilo), the sugar analyses of the chyle showed 0.36 per cent, 0.76 per cent, 0.39 per cent, 0.46 per cent. In dogs, the highest dose given was 40 g. ($6\frac{2}{3}$ g. per kilo), and the corresponding highest lymph-analysis was 0.52 per cent. In only two of the entire series of experiments with both rabbits and dogs did the lymph-sugar reach 0.5 per cent. Ginsberg concluded from his experiments that von Mering's results were not true in an absolute sense; that the blood-vessels do indeed absorb practically all the sugar from the intestine; but when very large quantities of sugar together with very large quantities of liquid are present in the intestine, a small fraction thereof may make its way past the blood-capillary layer of the villus, and be picked up by the lymphatics. Ginsberg is often cited as if he were the father of the lymphatic hypothesis of alimentary glycosuria. He did not mention the subject in his paper.

Schoenborn at Leube's suggestion studied the question of absorption of sugar into peripheral blood-vessels, to the extent

of one human experiment. His ordinary rectal infusions, even with such quantities of sugar as 174 g. and such quantities of water as 1000 cc., failed to cause glycosuria. But in a girl with chlorosis, aged 24 years, he introduced a rubber bag in such manner as to shut off the last 10 cm. of the rectum from the higher portion of the bowel, and thus assure that the entire dose of sugar should be absorbed by the middle hemorrhoidal vessels, and thus enter the systemic instead of the portal circulation. After much instrumentation, 18 g. dextrose in 150 cc. solution was given at 11 a.m. At 12 noon the rectum was cleansed and the bag removed; it was found that the sugar had been completely absorbed. The urine was collected 2-hourly. At 12 m. and at 2 p.m. it was negative. At 4 p.m. it contained 0.35 per cent sugar. The 6 p.m. and 8 p.m. urine contained traces, after which the reaction disappeared. In a patient with artificial anus after resection of the rectum, a control experiment with identical methods yielded negative results; that is, the sugar presumably entered the portal circulation, and there was no glycosuria. This work, in the opinion of Schoenborn, and of Leube, who suggested and directed it, proved the importance of absorption into the systemic vessels, for the production of glycosuria.

Schlesinger (1) found a lowered tolerance for dextrose in dogs after ligating the thoracic duct, and similarly after tying the bile-duct. But when this acute stage following thoracic-duct ligature had passed off, the animals showed a decided increase beyond the normal limits of sugar assimilation, and the author explained it as the result of closing the channel of lymphatic absorption, thus necessitating that all the sugar should pass to the liver.

None of the above work is valid. Bernard's interpretation of his experiments has been overthrown by the Eck-fistula results. Bock and Hoffmann's procedure has been proved unsuitable. The sugar concentration of the lymph found by Ginsberg, with the known rate of lymph-flow, is too slight to cause glycosuria; it may in fact be questioned whether sugar-absorption under anæsthesia is normal. Schlesinger's results are not to be explained as a blocking of lymph-absorption; Biedl has shown that ligature or fistula of the thoracic duct may radically derange the sugar-economy. Schoenborn's one human observation is evidently a case of slight nervous or traumatic glycosuria; the glycosuria did not begin till two hours or more after the complete absorption of the sugar, which is an impossibility in any form of alimentary

glycosuria. If correct, the result could not explain alimentary glycosuria; for it is inconceivable that out of the dose ordinarily given, 18 g. should be absorbed by the middle hemorrhoidal vessels or the gastric-œsophageal anastomoses; and if the absorption were by the lymph, according to Ginsberg's highest values, 3600 cc. of lymph would be required to absorb the 18 g. dextrose necessary for a mere trace of glycosuria.

Experimentally, the hypothesis of lymphatic absorption as an explanation of alimentary glycosuria is overthrown by the work of De Filippi, and later of Michaud, who found that the Eck fistula does not greatly lower the dextrose tolerance of dogs; also by the excellent utilization of large quantities of intravenously injected dextrose in the experiments of Biedl and Kraus and of Kausch and Berendes in human beings and of numerous investigators in animals. Pavy's interpretation of De Filippi's experiments, in favor of the view that sugar is synthesized in the intestinal wall into protein or fat, fails to explain the results of intravenous injections. The liver evidently does not possess the metabolic monopoly which in the past many have assigned to it. Folin and Denis have demonstrated that even the amino-acids largely pass through the liver and are used directly by the muscles. Though much sugar is doubtless held back by the liver, probably a considerable amount normally passes through it directly to the muscles. When the liver is sidetracked by means of the Eck fistula, the muscles perform well the labor of blood-sugar regulation. For alimentary glycosuria under normal conditions, it is necessary that the rapidity of absorption of sugar shall overtax the capacity of both liver and muscles, and shall then force the blood-sugar high enough to overcome the normal impermeability of the kidney. Lymphatic absorption, if any occurs, is negligible.

17. The Dextrose Paradox.

The "dextrose paradox," or the "paradoxical law of dextrose," is the term by which I shall designate that remarkable power of every non-diabetic organism to utilize dextrose in absolutely unlimited quantity. This fact is well established and occasionally mentioned, but has not yet received the full recognition which it deserves.

Hofmeister's term of "assimilation limit," and the equivalent "sugar tolerance," represent a concept possessing a certain amount of value in certain connections, and have been used for this pur-

pose in the preceding sections. But what is denoted by those terms is nothing more than that quantity of sugar which suffices to cause the excretion of some small trace in the urine. It should be understood that such limits are only apparent, not real. Of genuine limitations of the power of the normal organism to metabolize dextrose administered by any or all of the possible channels, absolutely none exist. If anyone asks the question, "What is the actual limit of assimilation of glucose in the normal organism?" the only answer is, "Death." For the amount of the sugar utilized is governed not by any restriction of power on the part of the organism; it is governed only by the dose. Give the sugar by any route; increase the quantity at pleasure; it is possible by sufficient dosage to kill the animal, but it is not possible to cause more than a fraction of the whole to be excreted in the urine.

One or two early writers imagined that sugar can be assimilated up to a certain amount, and above that amount, all the excess flows away through the kidneys quantitatively. Süssenguth (2) quotes Bunge as expressing this view. Linossier and Roque were perhaps the first to note the incorrectness of this very natural assumption. Schlesinger has emphasized that in alimentary glycosuria only a trifling fraction of the ingested dose is ever excreted. Yet it is curious how this long established fact has been ignored by the best-informed writers.

Von Noorden [(1), p. 21] mentions, as something difficult to explain on the basis of the prevalent theories, the question why the excretion of sugar does not keep pace with the increase in its ingestion. He gives the following interesting table, in which A and B are two normal individuals.

Dextrose ingested.	Excretion by A.	Excretion by B.
100 g.	0	0
150 g.	0.15 g.	0
180 g.	0.25 g.	0.23 g.
200 g.	0.26 g.	0.71 g.
250 g.	0.52 g.	0.64 g.

Yet von Noorden elsewhere [(3), p. 544] says: "The tissues will not consume a larger quantity of material than is required for their respective energies. If the glycogen depots are no longer active, the sugar which is not used up in the performance of work,

or in the production of fat, remains in the blood and tissue-juices, and is removed by the kidneys."

Abderhalden says in his text-book (p. 440): "Under normal conditions, it is not possible to increase the amount of oxidation taking place in the tissues by increasing the supply of oxygen and the amount taken up by the blood. Similarly, we are not able to increase the total consumption of material very much by increasing the supply of carbohydrate or fat."

Lusk (3) refers to the experiments and doctrines of Zuntz and of Rubner, upon which the current views are based.

Pflüger [(1), p. 410] says: "Es ist denkbar, dass der Zuckerverbrauch der Organe wächst mit Zunahme des Procentgehaltes des Blutes an Zucker." Yet a few pages farther on [p. 449] observe the following statement by the same author in the same book: "Nimmt die Zuckermenge des Blutes zu, so steigert das den Verbrauch nicht." The idea is more fully and forcibly conveyed by giving the statement in its complete context. "Als oberster Grundsatz des thierischen Stoffwechsels gilt, dass derselbe bedingt ist durch die Arbeitsgrösse der Organe, nicht durch die Menge der dem Organismus gebotenen Nahrung. Das gilt ganz besonders für die aus Fett oder Kohlehydrat bestehende Nahrung. Die kleine im Blut enthaltene Zuckermenge genügt zur Befriedigung des Bedürfnisse der Organe. Nimmt die Zuckermenge des Blutes zu, so steigert das den Verbrauch nicht. Desshalb wird der Zucker im Harne ausgeschieden. Führen wir in der Nahrung dem Diabetiker mehr Zucker zu, so steigern wir nur die ohnedies unbenutzbare Menge im Blute, wesshalb die Ausscheidung des Zuckers entsprechend wächst. Desshalb kann aber die Menge Zucker, welche der Organismus verwerthet, sehr gross sein. Man denke sich doch, dass Wasser, welches in ein bereits volles Glas gegossen wird, überläuft und damit nicht beweist, dass das Glas kein Wasser aufnehmen kann. Wenn der mit der Nahrung dem Diabetiker zugeführte Zucker wieder ausgeführt werden muss, also nicht oxydiert wird, ist es selbstverständlich, dass er keinen Einfluss auf den respiratorischen Quotienten ausüben kann."

A. E. Taylor calls attention to the fact that since the blood-sugar is increased in diabetes, by the law of mass-action we should expect increased glycogen-formation. The opposite is therefore all the more surprising.

The alleged physiological law of the non-dependence of utilization upon supply, and Pflüger's simile of a glass running over, are

contrary to fact. Taylor's suggestion of a law resembling mass-action is correct in the normal organism. In diabetes the glass not only runs over, but it is a Tantalus-glass; frequently more runs out than was poured in.

A question may arise as to what is meant by utilization; whether it includes both combustion and storage; whether the combustion is of normal or abnormal type. For the present purpose it is immaterial. Apparently what Pflüger laid down as "oberster Grundsatz des thierischen Stoffwechsels" is violated every time a carbohydrate meal is taken. Johansson showed how sugars increase the respiratory exchange, and different ones in different manner. Reicher and Stein have found increase of the quotient after ingestion of dextrose, the respiratory curve running accurately parallel with that of the blood-sugar. Gigon (2*A*) found the increase of CO_2 to be strictly proportional to the quantity of dextrose ingested; after ingestion of 100 g. dextrose the quantity of CO_2 was exactly twice as much as after ingestion of 50 g. dextrose. The increased combustion is not due to increased work. Johansson found it absent in diabetes. Zuntz and Mering, Wolfers, and Verzar have shown the increase with intravenous sugar-injections. McGuigan (4) in perfusion experiments proved that the sugar-consumption of mammalian muscles increases as the sugar-content of the blood rises. In recent papers from Lusk's laboratory [see Lusk (3) and Fisher and Wishart] the proof is furnished by calorimetry experiments that metabolism is increased by an increase of food-substances in the blood, following ingestion of either sugar or fat.* During the four hours required for full disposal of the sugar in these experiments, the higher metabolism present was shown by the respiratory quotient to be due to combustion of sugar. Thus there is demonstrated a normal increased combustion of sugar due directly to an increased supply of sugar. For the storage of sugar the case is equally well proved. The glycogen-content of liver and muscles is increased by sugar-feeding. In De Filippi's Eck-fistula dogs, the muscle-glycogen-content was that of overnutrition, while the percentage of liver-glycogen was that of starvation; in other words, the storage was governed by supply and not by tissue-requirements. The possibility was previously mentioned, that in case of great excess,

* The present discussion concerns only sugar. This work with fat, and recently elicited facts concerning amino-acids, apparently indicate a general law, that consumption of foods is increased by increase of the quantity in the blood.

sugar may also perhaps be disposed of by some abnormal process. In any event, the distinction between the diabetic and the non-diabetic organism remains clear. In the non-diabetic, the vastly greater part of any dose of dextrose is retained. Part of it is burned, as proved by the respiratory quotient. Part of it is stored as glycogen, and part evidently in other forms, for analysis does not account for the whole of the sugar that disappears. In the diabetic organism the reverse is true. In "total" diabetes, as after pancreas-extirpation, doses of sugar do not affect the respiratory quotient; they do not cause deposition of glycogen; they are quantitatively excreted. If diabetes consisted only in an increased production of sugar, these things could not be so. If only the power of glycogen-storage (formation or fixation) were lost, increased combustion must be demonstrable. If only the power of combustion of dextrose were lost, there must be a filling of the depots with glycogen. In actual fact, both of these powers are lost, and the dextrose saturates tissues which are starving for it and yet unable to make use of it. It is easy to demonstrate that in the various forms of glycosuria due to over-production of sugar, these rules hold; no matter how much sugar is being spontaneously excreted, the power to retain and dispose of injected dextrose is still absolutely unlimited; merely an increase of dose is necessary to obtain increased utilization. By the simple test of this paradoxical law of dextrose, the theory that diabetes is solely an over-production of sugar — a glass running over — falls down.

Nor is this all. The behavior of the kidney requires mention here. Von Noorden, in the quotation given, takes it as perfectly natural that the excess of unused sugar should flow off through the kidneys. In another place, he conceives of cases of diabetes in which the blood-sugar is not demonstrably increased, because the regulating action of the kidneys is so perfect that the excess is removed as quickly as it appears. Pflüger looked upon the glass running over as a good comparison. Pavy has always emphasized the rôle of the kidney as a regulator of blood-sugar. This general conception and expression, of the kidney playing a part very much like a dam, and regulating the height of the blood-sugar by allowing the excess above a certain level to flow off in the urine, is still common in the literature. For the normal organism it is false. By intravenous injection of dextrose it is possible to obtain a considerable glycosuria, for reasons to be

discussed in Chapter VI. There is also a considerable excretion of sugar in certain experimental forms of glycosuria, in which a nervous or other abnormal influence acts upon the kidney. But the effects of simple excess of circulating dextrose can be tested by the oral, subcutaneous or intraperitoneal administration of dextrose. The glycemia may be raised, by doses moderate in quantity or concentration, to the average diabetic level; or it may be forced up by larger doses to higher levels, as 0.85 per cent in one of my animals (Cat 59). The fact remains that only a comparative trifle is excreted through the kidneys; and to speak of the kidneys in a normal animal as "regulating" the percentage of blood-sugar is absurd. The immensely greater portion of the sugar is removed from the blood by the tissues; the effective "regulation" of the glycemia is a process resembling though not necessarily identical with mass-action, whereby the utilization or storage in the tissues is increased not merely in accordance with the working-needs of the tissues, but in accordance with the increase in the supply of sugar. In diabetes the kidney is a regulator. In an uncomplicated case, the glycemia is not likely to be found as high as 0.3 per cent, because the kidneys actively excrete the surplus to the best of their ability, and in a quantity which may be many ounces per day. No degree of hyperglycemia, resulting from introduction of dextrose by any or all of the three routes mentioned, can ever force the non-diabetic kidney to that massive excretion which even a moderate hyperglycemia occasions in the diabetic. To assume a simple increase of sugar as the cause of diabetes requires therefore a second assumption, viz., an altered activity on the part of the kidney.

We may express the facts otherwise by saying that in the non-diabetic, the limit of assimilation is only apparent; in the diabetic, it is real. In the non-diabetic, though there be alimentary glycosuria, the motto is still *plus ultra;* the capability to utilize an unlimited increase of the given dose still remains. In the diabetic, on the contrary, it is *ne plus ultra;* the assimilation is at its limit, and the excess will flow off through the kidney, unless the kidney is disabled. The distinction is absolute. It is not superficial nor accidental, like other supposed tests of diabetes. It is essential and fundamental, and has its origin in the very nature of the change which constitutes diabetes. It furnishes a demonstrable and absolute theoretical distinction between diabetes and every other form of glycosuria. For practical clinical purposes

its usefulness is restricted, because such a use often applies to patients with only a trace of diabetes, in whom the normal power of carbohydrate-disposal is largely retained. To the extent that he is diabetic, the patient's limit of sugar-tolerance must be real and not apparent. If 50–100 g. dextrose causes glycosuria, then 200–300 g. will perhaps produce a greater increment of excretion in incipient diabetes than in other forms of alimentary glycosuria, especially on repetition of the dose. In the laboratory, the paradoxical law, with a related test to be discussed in Chapter VI, furnishes an absolute theoretical and practical distinction between diabetes and every other form of experimental glycosuria.

CHAPTER II.

ADMINISTRATION OF CARBOHYDRATES OTHER THAN DEXTROSE.

1. Comparative Assimilation Limits by Mouth.

THE findings of several investigators with respect to the common sugars are conveniently tabulated by Linossier and Roque as follows, the sugars being arranged in order of the ease with which they give rise to mellituria.

Hofmeister (dog).	Worm-Müller (man).	Moritz (man).	Linossier and Roque (man).
Galactose	Glucose	Lactose	Saccharose
Lactose	Saccharose	Saccharose	Glucose
Glucose	Lactose	Glucose	Lactose
Levulose	Levulose		
Saccharose			

The following is the order found by Brocard, and confirmed by Charrin (ref. by De Filippi):

Levulose.
Galactose.
Glucose.

De Filippi (1) has treated the subject of the tolerance in dogs. He publishes a table compiled by Quarta, in which the average tolerance of male dogs was 4.06 g. per kilo for dextrose and 3.11 g. per kilo for levulose; and of female dogs was 10.28 g. per kilo for dextrose and 3.58 g. per kilo for levulose. De Filippi's own tests resulted as follows, the figures being the amount required to cause alimentary mellituria in 12-kilo dogs:

Lactose	10 g.
Levulose	20 g.
Saccharose	40 g.
Glucose	125 g. or more.

The following table for man is given by von Noorden [(1), p. 20], and is probably entitled to the greatest confidence, because

of the wide experience of the author. Sugar is said to appear in the urine after ingestion of:

Galactose	about 20 g.
Lactose	more than 120 g.
Levulose	120–150 g.
Dextrose	150–180 g.
Saccharose	150–200 g.

It is necessary to add, however, that the French use cane-sugar as a test more than the Germans; and Linnossier and Roque report sugar in the urine from as little as 50 g. saccharose, and in this they are in accord with Worm-Müller; and lately Le Goff has published a test of sixteen healthy men with 100 g. saccharose in a glass of water in the morning, and every one of them showed both saccharosuria and glycosuria. In the case of levulose also, there is much question concerning the assimilative power.

The widely varying results of different authors may perhaps be explained as due to:

1. Differences in methods, including such things as the length of time the patient has fasted, the amount of water taken with the sugar, etc.

2. Impurities of sugars. Krause and Ludwig (ref. by Linossier and Roque) found that 100 g. impure glucose caused glycosuria when 200 g. pure glucose caused none.

3. False conclusions drawn from appearance of faint traces of sugar in urine.

4. Individual and perhaps racial differences. How wide the individual variations may be is shown in Linnossier and Roque's finding that 5 out of 17 human subjects showed sugar in urine after 50 g. saccharose, while 17 out of 19 showed it after 300 g. To cause glycosuria in the most resistant subjects required 350 g. saccharose.

Accurate tests, as heretofore mentioned, require (1) uniform methods, especially as regards fasting and dilution; (2) the rejection of faint traces, and the acceptance as positive of only those cases excreting quantitatively determinable amounts (Naunyn); (3) for the highest accuracy, a test whether an increased dose increases the excretion (Schlesinger).

For starch the tolerance is ordinarily without limit. But inasmuch as dogs after prolonged fasting, or human patients suffering from fever or alcoholism, may exhibit glycosuria after ingestion

of starch, it is clear that glycosuria *ex amylo* is not a decisive test for diabetes. However useful it may be ordinarily, it does not strike down deep to any absolute, fundamental distinction between diabetes and non-diabetes, and its results in doubtful cases are therefore necessarily open to more or less question.

Tolerance for dextrins appears never to have been tested. They should possibly show a greater tendency to influence the urine than starch. The mellituria of rats after eating bread has been mentioned, and the few reports concerning dextrinuria will be discussed in Section 8 of this chapter.

Pentoses and the rarer carbohydrates are here omitted. The facts concerning them are given in the book of Rosenberger.

2. Saccharose.

As the most commonly used sugar, saccharose deserves first place in the discussion of individual members of the group. Dextrose affords a somewhat better test of the sugar-tolerance. But since the average patient is likely to take more sugar as saccharose than in any other form, there is a legitimate interest in the question of how he assimilates this particular sugar. Thus Le Goff, whose recent discovery of both saccharosuria and glycosuria in 100 per cent of cases after 100 g. cane-sugar, raises the question whether the use of this particular sugar, which has little place in the dietary of primitive man, contributes anything to the increased incidence of diabetes mellitus.

The sugar that appears in the urine, after ingestion of cane-sugar in excess, may be either saccharose, invert sugar, or both. The conditions determining the appearance of one or the other are unknown. Claude Bernard [(3), p. 320] mentions the appearance of invert sugar in the urine of dogs after heavy cane-sugar feeding. Lepine [(1), p. 90] notes the presence of cane-sugar in the portal blood of dogs after large doses. My brief experience with saccharose feeding in dogs has inclined me to the opinion that the quantity and proportions of the sugars—saccharose and invert sugar — excreted may depend largely on the digestive condition — whether the sugar is introduced on an empty stomach, or at different stages of digestion. By some, saccharose feeding has been used as a clinical test of diabetes, the authors asserting that diabetics excrete dextrose, and non-diabetics saccharose. The distinction is not perfect.

Perfusion experiments of livers by Grube and others, and of muscles by Hatcher and Wolf, have proved that saccharose is not a direct glycogen-former. Texts [Magnus-Levy (4), p. 25; Pflüger (1), pp. 201–205] state loosely that parenterally injected saccharose is quantitatively excreted. The statement is not exact, for saccharose is not on a par with lactose in this respect. The greater part is excreted unchanged, at least by mammals. Different species probably utilize it in different degree. Furthermore, there is a saccharose paradox; the utilization increases with the dose. The dog occupies a unique position, as the only species in which reducing sugar appears in the urine in consequence of parenteral injection of saccharose. Brugnola is said to have observed utilization after intravenous injection in birds. It is to be expected that birds and selachians will show a higher utilization than mammals; experiments with subcutaneous injections might show some interestingly high percentages.

A review of part of the literature dealing with parenteral injections of saccharose is as follows.

Claude Bernard (Inaugural dissertation) injected cane-sugar intravenously in dogs, and found it excreted quantitatively in the urine. He devoted care to proving that this occurred even with very small doses. The doctrine of the quantitative excretion of cane-sugar thus had its beginning. If Bernard had tried the opposite procedure, and injected *large* quantities intravenously, he would have found reducing sugar in the urine.

C. Voit, and following him Cremer (1), showed that only those sugars which are fermentable by yeast are utilized and form glycogen in the animal body.

Emil Fischer and Niebel proved that the blood-serum of various species (horse, beef, sheep, rat, chicken, goose, frog, etc.) has no power to invert saccharose.

Fritz Voit [(1), but especially (2)] published a classical work concerning the subcutaneous injection of a number of different carbohydrates in human patients. He made four injections of saccharose, ranging from 25 g. down to 1.267 g., and found that the excretion in every instance was "as good as quantitative." The fact that with the largest injection nearly a gram of sugar remained unaccounted for, could be interpreted as within the limits of operative error, but probably represents actual utilization of a small fraction of the dose. As man holds the lowest position among mammals in his power to

utilize dextrose, he perhaps occupies a similar place as respects saccharose.

Kossa (1) wished to study the pharmacology and toxicology of the sugars, and made use chiefly of saccharose. In a few cases he employed dextrose, and concluded that the effects of the two are practically identical. The similarity holds only so far as the osmotic effects are concerned.

Pavy (3), after intravenous injection, found by extensive analyses of blood and urine that saccharose was very quickly excreted.

Blumenthal found in the rabbit, that where the intravenous "saturation limit" for dextrose was 2.7–2.8 g., that of saccharose was 0.3 g. This is, of course, very small; but if the limit of assimilation for saccharose by other parenteral routes were found to be always one-ninth that of dextrose, the utilization would be by no means small.

Although the blood-serum of the normal dog contains no ferment capable of inverting saccharose, Weinland was able by repeated subcutaneous injections of saccharose to cause an invertin to appear in the serum; that is, the serum gained the power to invert saccharose in vitro. In a litter of puppies he found, moreover, that the power to utilize saccharose markedly increased with repeated injections. Quantitative results were not attempted, for the puppies could not be kept long enough away from their mother. But tests of the urine showed that, *in spite of increasing doses*, the quantity of saccharose in the urine steadily diminished till only a trifle was present. The blood-serum as usual showed inverting action in vitro.

Weinland's artificial production of a new ferment in an animal's serum is interesting biologically and from the standpoint of carbohydrate economy. The supposed increased power of the puppies to utilize saccharose seems explainable as follows. Weinland, assuming the saccharose to be excreted unchanged, examined the urines only by the polariscopic method; his work contains no mention of reduction tests. In the case of the puppies, the doses were steadily increased; the quantity of sugar revealed by the polariscope steadily decreased. Anyone can easily satisfy himself that increased doses cause increase of levo-rotatory reducing sugar. The polariscopic results are obvious.

Abderhalden and Brahm, without knowledge of Weinland's work, were able similarly to call forth an invertin-production in

the serum. Abderhalden and Kapfberger studied the question more carefully; but the results must be treated in Section 12 of this chapter.

The rabbit has no invertin in its normal serum; nor does it ever, as does the dog, excrete reducing sugar after parenteral introduction of saccharose. But corresponding to its high power of dextrose assimilation is its power of burning saccharose; a power which may equal or surpass that of the dog. Hohlweg and Voit found the following values after subcutaneous saccharose injections in normal rabbits:

Injected	Excreted
20.915g.	20.206g.
19.882g.	19.294g.

By superheating rabbits they found the following values:

Injected	Excreted
20.968g	16.034g.
20.968g.	19.932g.
19.822g.	15.926g.
19.822g.	16.621g.

Hohlweg alone obtained the following values in a dog.
At rest:

Injected	Excreted
15.2475g.	14.801g.
15.2475g.	14.834g.

By running in treadmill:

Injected	Excreted
15.2475g.	13.908g.
"	10.393g.
"	11.1948g.
"	12.2892g.

Thus, an exercising dog is seen to be able to utilize a maximum of almost 5 g. saccharose, or almost a third of the quantity injected. By suitably increasing the dose so as to take advantage of the "saccharose paradox," the dog might doubtless be made to burn a considerable quantity of cane-sugar.

Heilner (6) injected normal rabbits with cane-sugar in 10 per cent solution subcutaneously, and obtained utilization far higher

than that of Hohlweg and Voit. Heilner's normal values are expressed in the following table.

Injected	Excreted	Retained
31.3668g.	24.7397g.	6.6271g.
31.850g.	30.746g.	1.104g.
29.2435g.	27.607g.	1.6365g.
30.176g.	25.595g.	4.581g.

Such a utilization is of course by no means insignificant.

Mendel has reported that saccharose injected subcutaneously or intraperitoneally in dogs, cats, and rabbits may reappear in the urine to the extent of more than 90 per cent of the quantity injected. Neither repeated parenteral injections, nor starvation, lead to any increase of utilization.

Jappelli and D'Errico (quoted by Mendel and Kleiner) found in experiments on dogs that when cane-sugar is injected directly into the circulation, the quantity eliminated in the urine is never equivalent to the amount injected. Both glycosuria and saccharosuria result, the former ceasing first. The blood has no inverting action. They further found that after intravenous or subcutaneous injection, saccharose is excreted into the alimentary tract through the salivary glands, the gastric mucosa, and, in insignificant degree, the bile.

Mendel and Kleiner injected 3 g. saccharose into the peritoneum of a small dog, and recovered only $1\frac{1}{2}$ g. in the urine. They note that a reducing levo-rotatory sugar appeared in the urine of some, not all, of the dogs receiving saccharose parenterally. [This is because of the comparatively small dose, generally about 1 g. per kilo. Larger quantities invariably cause positive reduction.] The tables which they present are too long to reproduce here, but the figures show a considerable range. A fair summary is that in the dog, 25 to 35 per cent of the total quantity injected is generally assimilated. In a minority of instances, the assimilation was very slight. But in another minority, the assimilation was half or more of the quantity injected. In cats, their table shows the quantity of sugar excreted ranging all the way from 44 per cent to 90 per cent of the amount injected; on the whole, therefore, a considerable utilization. The urine of cats never showed reduction. Utilization in puppies was no better than in adult dogs. Repeated injections sometimes resulted in a slight inverting power of the serum, but results were generally negative. Intraperitoneal injections caused sugar to appear in the urine in 5 or 10 minutes.

Excretion was complete within 36 hours. Injections at intervals, of about 1 g. per kilo, intraperitoneally into a dog for 7½ weeks caused no increase of utilization. Repeated injections in a cat were similarly negative. They therefore fail to confirm Weinland. Other tests showed that age, pregnancy, fasting, and alcohol had no influence upon the utilization.

The publications concerning injections of saccharose from the standpoint of diuresis will be considered in Chapter VI. These investigators did not concern themselves with the question of utilization.

My own saccharose injections have been performed for other purposes, but a few incidental observations may be here noted, especially concerning reducing sugar.

Cat 21 (weight 3½ kilos). Daily subcutaneous saccharose injections (generally 20 g. daily; sometimes 10 g.) were given from June 17 to September 8. Reducing sugar was never found in the urine. At autopsy, the intestinal contents were negative for both reducing and cane-sugar, though the bowel contained liquid which apparently represented glandular secretions. The gastro-intestinal excretion of saccharose was therefore not confirmed in this instance.

Dog 17 on February 27 received a subcutaneous injection of 23.5 g. saccharose (2½ g. per kilo). The excretion of reducing sugar was less than usual; titrated as dextrose, it was 0.2 per cent or 0.49 g.

Dog 18 (weight 8 kilos) on December 3, while fasting, received an intravenous injection of 5 cc. 80 per cent saccharose. Though the dose was so small, the urine gave a slight reduction test. On December 14, subcutaneous injection of 10 g. saccharose per kilo, while still fasting, again caused excretion of reducing sugar. On May 30, a faint reduction-test appeared in the urine after subcutaneous injection of 7.88 g. saccharose (1 g. per kilo), and this reduction increased with the larger injections of June 3 (3 g. per kilo) and June 7 and 12 (5 g. per kilo), though the highest percentage was only 0.5 per cent.

Dog 21 (weight 6900 g.) on June 27 received an intravenous injection of 25 g. saccharose. The total reducing sugar excreted, titrated as dextrose, was 1.511 g. The saccharose excreted, titrated after inversion, was 21.819 g. As the quantity injected was determined only by weight, the utilization cannot be figured exactly.

Dog 34 (weight 6400 g.) on April 14 received a subcutaneous injection of 19.2 g. saccharose (3 g. per kilo). Here reducing sugar, calculated as dextrose, was excreted to the amount of 1.1 per cent or 2.31 g.

Dog 186 (weight $9\frac{1}{2}$ kilos) on January 19 received an intravenous injection of 30 g. saccharose (about $3\frac{1}{5}$ g. per kilo). The excretion of reducing sugar, reckoned as dextrose, amounted to 2.215 g. On January 22, 60 g. saccharose was injected subcutaneously. In one specimen of urine the reducing sugar, titrated as dextrose, reached 2.4 per cent; the total excretion was 7.28 g.

Dogs apparently vary somewhat in their tendency to excrete reducing sugar after saccharose injection. Saccharose excretion regularly continues longer than the excretion of reducing sugar.

3. Lactose.

Lactose is the next important disaccharide of food. It is the one distinctive animal sugar, — though present in a very few plants, as has recently been shown, — and surprise is therefore justifiable when it proves itself the one sugar which all the tissues, tissue-fluids, and secretions of the body attack with the greatest difficulty of all. A number of lower organisms can ferment it, but yet it must rank in general among the least fermentable of all sugars. Its relative invulnerability to attack of every general sort may be a special provision of nature to convey it safely on its special physiological journey, viz., from the special cells of the mammary gland, which produce it, to the special cells of the infant's small intestine, which attack it. A relationship of something like symbiotic importance has grown up on the basis of the peculiarities of lactose. For the organisms which ferment lactose and the acids which they form from lactose are the special agents causing milk to undergo harmless souring instead of harmful putrefaction; and the same or similar organisms constituting the intestinal flora of the healthy milk-fed infant assist in its normal processes of digestion, and contribute to suppress the growth of putrefactive or pathogenic organisms. To the peculiarities of lactose and the organisms that ferment lactose is preëminently due the recently heralded therapeutic value of sour milk, buttermilk, and certain milk-souring bacteria.

Concerning the digestion of lactose, more is still guessed than proved. In some manner it is split into its components, dextrose and galactose, somewhere between the intestinal lumen and the

circulation; and the common belief is that this hydrolysis is a special function performed within the epithelial cells of the intestinal mucous membrane. The work of several investigators, including Fischer and Niebel [see also the literature in Voit (2)], who have demonstrated a splitting of lactose by scrapings or extracts of the duodenal mucosa, support this view. If such is the case, Höber's suggestion, that sugars present in excess may sometimes be absorbed through the interstices between the cells, would be important if true; for lactose might thus escape the splitting process in the cells and enter the circulation as the useless disaccharide.

The assimilation limits of lactose are low, as mentioned in the first section of this chapter. They are higher when the lactose is given in the form of milk than when it is given pure. The question is proper whether substances not foodstuffs could modify the tolerance in this manner. The lactose seems to cling with especial tenacity to the casein. Sugars in general are adsorbed by proteins and similar substances. Various authors examining blood, feces or other mixtures for sugar, note the unequal distribution between the liquid portion and the solid masses; careful and repeated washing is necessary to separate all the sugar. But in milk the binding is more tenacious, for repeated washing, and repeated solution and reprecipitation of the casein, free it from the lactose only very slowly and imperfectly. Pflüger, in his critical examination of Lüthje's proof of the formation of sugar from protein in diabetic dogs, tested the "chemically pure" casein of the market, and found it to contain lactose. [See also Pflüger (1), pp. 277–78.] Linkings of this nature, even if nothing more than a form of adsorption, may well play a part in the digestion, absorption, and utilization of foods. They may help to explain why milk under a variety of conditions behaves differently from any other food.

Ingestion of lactose beyond the limit of tolerance causes the appearance in the urine of lactose, galactose, or both. Here again, as with cane-sugar, the particular state of the bowel or stage of digestion may perhaps determine the relations between hydrolysis and absorption.

Practically all lactose arriving in the circulation as such is excreted unchanged in the urine. The lactosuria resulting from the escape of small quantities of milk-sugar into the circulation of young infants and of pregnant or lactating women has been men-

tioned. In the latter, it may be increased by dextrose feeding. Eichhorst witnessed lactosuria after nutrient enemas of milk. Fritz Voit demonstrated the quantitative excretion of lactose injected subcutaneously into human subjects. Neither Pavy (3) nor McGuigan (3) demonstrated the utilization of any lactose after intravenous injection. Blumenthal found by his intravenous method that where, in a rabbit, the saturation limit for dextrose was "above 2.3 g.," that for lactose was 0.25 g. If this could permit the interpretation that the assimilation limit of lactose is about a tenth that of dextrose, it would imply no small utilization; but the results cannot be accepted in this sense.

Hohlweg and Voit give the following table for subcutaneous lactose-injections in rabbits.

Injected g.	Excreted		Duration of Excretion in hours
	Grams	Percent.	
At Room Temperature:			
10.673	10.391	97.37	24
With over-heating:			
10.673	10.073	94.38	23½
12.990	12.434	95.73	24
16.000	15.192	94.95	23½

They conclude that a distinct effect from over-heating cannot be demonstrated, since the differences still lie within the limits of technical error. Nevertheless the figures indicate at least the possibility that a slight assimilation of lactose occurred.

Hohlweg in a dog gained negative results as follows.

Injected g.	Excreted		Duration of Excretion in hours
	Grams	Percent.	
At rest:			
21.88	21.92	100.19	24
21.88	21.76	99.45	24
With work in treadmill:			
21.88	21.792	99.59	24
21.88	21.903	100.1	23

These give the impression of actually negative results.

In my experiments with injection of lactose (performed for other purposes), the quantity injected has been determined only

by weight, and the estimations in the urine have been only accurate enough to give information as to the relative proportions excreted in different specimens. The duration of excretion may be worth mentioning. Dog 17 on January 20 received a subcutaneous injection of 85.5 g. lactose (10 g. per kilo). The duration of excretion was between 36 and 48 hours. Dog 18 on June 28 and on July 7 received subcutaneous injections of 112 g. lactose (15 g. per kilo). After the first injection, the excretion of lactose was very pronounced for 48 hours, distinctly positive for another 12 hours, and was not found entirely negative till 70 hours from the time of injection. This was a case in which a limited quantity of water was given regularly by stomach-tube. After the second injection, the excretion was ended within 36 hours from the time of injection; in this instance free drinking was permitted. Dog 21 on May 30 received a subcutaneous injection of 1 g. per kilo; excretion lasted less than 24 hours. On June 3 the same dog received 3 g. per kilo; excretion was finished within 24 hours. On June 7 the same dog received 5 g. per kilo; excretion lasted about 30 hours.

Birds may reasonably be expected to utilize lactose better than mammals. It would seem worth while to reinvestigate the utilization in the latter, in order to determine whether any lactose is consumed, whether there is a lactose paradox, and, therefore, whether the normal organism shows even toward lactose that total inability to utilize which the "totally" diabetic organism shows for dextrose. In such a research, the largest convenient doses should be advisable, because (*a*) differences of grams are less subject to technical error than differences of fractions of grams; (*b*) the duration of excretion, *i.e.*, the time during which the tissues can act on the lactose, is greater; (*c*) according to the law of other sugars, utilization should increase with dosage. If utilization of lactose is possible at all, it is safe to predict that a lactose paradox will be demonstrable.

4. Maltose.

Maltose is the only one of the common sugars for which no accurate tests of the tolerance exist. It is not as important a constituent of the diet as saccharose and lactose. But it is present in beer, and for that reason is held responsible for one of the relatively frequent forms of alimentary mellituria, namely that which is found after heavy beer-drinking; whether the excreted

sugar is maltose is unknown. It has the reputation of being the sugar which in diabetes is generally borne worse than any other.

Pflüger [(1), pp. 374–75] notes that Pavy found maltose present in the liver, as one of the intermediate stages between glycogen and glucose; and that Külz found maltose present with iso-maltose.

That traces of a maltose are supposed to be present normally in blood was mentioned in Chapter I; also that Spallita found considerable maltose along with the dextrose of turtle-blood, and attributed its presence to the slow stages of glycogenolysis in that animal. As mentioned, a small part of the carbohydrate of normal urine has been described as maltose; Oppler's work may introduce a doubt on this point. Pathological maltosuria is a rare human anomaly. The presence of maltose along with dextrose in diabetic urine has been repeatedly asserted. Lepine [(1), p. 353] mentions its presence in the urine of depancreatized dogs. Geelmuyden has studied the question extensively. In his closing paper, he lays stress above all upon the difficulties and uncertainties of the necessary technical methods. His final conclusion is that maltose is never present in diabetic urine. The majority of investigators have arrived at the opposite conclusion. Theoretically, maltosuria should be expected in advanced cases of diabetes. In a disease which shows in later stages not only enormous quantities of dextrose but also a surprising amount of dextrin in the urine, and free glycogen in the blood-plasma, it would be surprising if the other step in glycogen break-down, namely maltose, did not enter the urine, and probably before the dextrin enters it.

Pavy [(3), p. 482] quotes from Phillips, that maltose injected intravenously is excreted as such, but injected subcutaneously is excreted partly as maltose and partly as dextrose. Pavy's own careful analyses are instructive. Schmidt and Meyer claim that maltose injected intraperitoneally is quantitatively excreted. This mistake is perhaps accounted for by a partial elimination as dextrose, thus confusing the analysis.

Blumenthal did not include maltose in his study of intravenous saturation limits. McGuigan (3), injecting intravenously a 0.5 per cent solution at the rate of 1 cc. per minute, found 45 cc. necessary to cause maltose to enter the urine (as compared with 40 cc. dextrose). This result does not correspond to the known limits of maltose tolerance by other channels of administration.

It probably indicates one of those frequent differences between assimilation as tested by the intravenous and by other methods.

Fritz Voit gave two injections of maltose in human patients; one of 8.789 g., the other of 27.756 g. The urine remained sugar-free.

Hohlweg and Voit found the following values after subcutaneous injections of maltose in rabbits.

	Injected g.	Excreted g.
At room-temperature:	17.642	9.24
	"	8.006
	"	13.286
With over-heating:	17.642	4.24
	"	11.308

Hohlweg found the following results from subcutaneous injections in a dog.

	Injected g.	Excreted g.
At rest:	90.56	33.92
	"	28.944
With work in treadmill:	90.56	16.88
	"	18.1

The limits of maltose tolerance in animals is an uninvestigated subject. I have made a few observations as follows.

Cat 18 (weight 2230 g.) on June 17 received a subcutaneous injection of 4 g. maltose. The urine showed rather heavy reduction. The tolerance was evidently much less than 2 g. per kilo.

Rabbit 36 (weight 1200 g.) received a series of maltose injections. The lowest dose was 4 g. The urine gave moderate or heavy reduction. The indication is that the rabbit, with its high dextrose tolerance, has a maltose tolerance of less than 3 g. per kilo.

Dog 18 on June 15 received a subcutaneous injection of 1 g. maltose per kilo. The urine remained sugar-free. On June 19, a subcutaneous injection of 3 g. maltose per kilo in the forenoon caused a very slight reaction in the urine, lasting only till evening. On June 22, a subcutaneous injection of 38.25 g. (5 g. per kilo) produced an excretion of 1.05 g. The tolerance in the dog is therefore between 1 and 3 g. per kilo.

It is interesting to note, in the case of a large injection like Hohlweg's, how high the excretion rose. But it is evident that the number of grams utilized is greater with a larger than with a smaller dose. There is, therefore, a maltose paradox.

5. Levulose.

That traces of levulose occur in normal blood has already been mentioned. Pathological human levulosuria will be considered in Chapter VIII, as also the glycogen formation from levulose. The present topic deals chiefly with the tolerance.

Concerning the normal oral tolerance of levulose it is difficult to form a satisfactory idea. In von Noorden's table, 150–180 g. being the normal dextrose tolerance, the normal tolerance of levulose is 120–150 g. Strauss found that normal human beings regularly assimilate 100 g. levulose perfectly. Other authors previously mentioned have found lower limits. With animals there is equal disagreement. Reports vary from the statement of Donath and Schlesinger that levulose is tolerated about the same as dextrose, to that of De Filippi, who found the tolerance of 12-kilo dogs to be 125 g. dextrose but only 20 g. levulose. Hohlweg (ref. by Wehrle) found repeatedly that 10-kilo dogs may excrete sugar after the feeding of 10 g. levulose. The discrepancies may perhaps be to some extent explained by differences in the standard of tolerance. Traces of levulose generally appear in the urine very easily; but if traces are disregarded, a considerable increase of dosage may be necessary to cause any well-marked excretion.

It is matter of common knowledge that the pancreas does not play such a rôle for levulose as it does for dextrose. Depancreatized dogs form glycogen from levulose, when they cannot form it from dextrose. As noted in Chapter VIII, the distinction is not peculiar to diabetes. But there is evidence that the liver does stand in some special relation to levulose metabolism. There is no evidence that the muscles can form glycogen from levulose, and the experiments of Sachs with dehepatized frogs are interpreted to the contrary. On the other hand, the ability of the muscles to burn levulose seems well established. Sehrt found that a pancreas-muscle mixture is able to decompose dextrose but not levulose; Hall confirmed this by finding that the mixture destroys glucose, but not levulose, lactose nor arabinose. As usual, such a procedure seems not to give a correct idea of the processes in the living body. McGuigan (4) perfused surviving livers and hindlegs of cats and dogs with diluted blood of the same species, to which various quantities of various sugars were added. Though the results apply to other sugars than levulose, the work is best

considered as a whole, and the author's conclusions are here presented verbatim.

"1. The living muscles of an animal when perfused with dextrose, levulose, or galactose cause a rapid oxidation of these sugars.

"2. The results with maltose would indicate that little if any of it is oxidized directly by the muscle.

"3. Increasing the amount of sugar in the perfused blood increases the amount oxidized.

"4. Stimulation of the muscles during the perfusion increases the oxidation.

"5. The perfusion of dead muscles shows practically no loss of sugar.

"6. Both in living and dead tissues perfusion causes an edematous condition. This occurs very much sooner and to a greater degree in the dead tissues.

"7. The perfused liver also utilizes the common sugars. It is probable that this will hold for all glandular organs.

"8. The glycogen-storing function of the liver is lost in perfusion much sooner than the sugar-destroying function. The same statement holds for the muscle.

"9. The glycolysis occurring in drawn blood at 40° C. in two hours is very small in amount."

The apparent importance of the liver for the utilization of levulose forms the basis of its introduction as a liver-test by Strauss. Alimentary glycosuria is of no significance for this purpose. But Strauss (2 and 3) reported that normal persons and patients with non-hepatic disorders assimilate 100 g. levulose completely, while about 80 per cent of all liver-cases react with levulosuria. For the literature of the subject, reference may be made to Weintraud (2) or the more recent work of Rosenberger. Lepine [(1), p. 227 ff.] reports confirmatory experiences. The levulose test, once rather generally accepted, is now somewhat less favorably considered, and is ranked as an occasionally useful accessory test. Falk and Saxl include it as one of a series of tests of the hepatic function. Schmidt found its value questionable; the tolerance for levulose was lowered in various unrelated diseases (pneumonia, scarlatina, erysipelas, diphtheria, etc.). Pollitzer has recently declared disbelief in the levulose or any other sugar-test of the hepatic function.

Aside from the apparent limitation to the liver of the power of forming glycogen from levulose, the principal experimental justification of the Strauss test is found in the work of De Filippi. In Eck-fistula dogs, this author found the levulose-tolerance reduced to a far greater degree than the dextrose-tolerance. Wehrle came to a different result with experiments on geese. Normal geese assimilated 40 g. dextrose perfectly; higher doses were not tried.

The normal tolerance for levulose was 13 g. In a series of geese the portal vein was ligated; they endured the operation perfectly. Afterward, there was complete assimilation when the following respective doses were fed: dextrose 40 g., maltose 40 g., saccharose 40 g., starch 50 g., or levulose 20 g. There was rather heavy mellituria after 40 g. levulose, and a trace after a mixture of 20 g. dextrose and 20 g. levulose. The author's general conclusion was that the value of the levulose test is questionable. He suggested that the difference between his experiments and those of authors who removed the liver might lie in an internal secretion of the liver, perhaps important for levulose metabolism. The results are not simple in application, because of the differences between birds and mammals, the fact that portal ligation does not entirely exclude the liver, and especially the interference with intestinal absorption. The considerable *increase* of levulose tolerance observed is evidently the result of retarded absorption.

The parenteral tolerance of levulose is calculated to furnish some valuable information. The analyses of Pavy (3) are the most complete for the question of what becomes of the levulose after injections of moderate quantities intravenously. A considerable part is utilized. Blumenthal found that where the intravenous saturation-limit of dextrose was 2.6–2.7 g., that for levulose was 2.5–2.7 g. In another rabbit, where the saturation-limit of dextrose was 2.2 g., that of levulose was 2.4 g. McGuigan (3), working with 0.5 per cent solutions flowing into the jugular vein at the rate of 1 cc. per minute, found that 80 cc. of levulose solution was received before reduction appeared in the urine (as compared with 40 cc. dextrose). As stated elsewhere, these results by the intravenous method differ from those gained by other methods. Neither orally, subcutaneously, nor intraperitoneally does the tolerance of levulose equal or exceed that of dextrose.

A distinctive toxicity has been reported in connection with parenteral levulose injections [Hedon and Arrous; Lepine (1), p. 203]. Rapid intravenous injections of 25 per cent sugar solutions in rabbits, to the amount of 15 g. per kilo of dextrose or saccharose, produced no marked injury. But levulose under these conditions was found fatal in doses of 14 to 15 g. per kilo. Also a combination of dextrose and levulose, either as invert sugar or as an artificially prepared mixture, is asserted to be more toxic than either dextrose or levulose alone. Doses of 8 to 10 g. per kilo

are said to cause death. Addition of saccharose is said to have a distoxicating effect. As the method of disposal of different sugars in the body is supposed to be different but is poorly understood, a further study of these toxic phenomena might be of interest.

Fritz Voit presented the following table of his subcutaneous levulose injections in human patients.

Injected g.	Excreted g.	Duration of Excretion in hours
10.13	Traces	---
10.94	0.99	11¼
31.25	Traces	5¢

Achard and Weil (ref. by Rosenberger) found traces excreted after subcutaneous injection of 10 g. levulose in man.

There seem to have been no tests of the assimilation limits of subcutaneously injected levulose in laboratory animals. Some of my experiments are as follows.

Rabbit 35 (weight 1200 g.) belonged to a lot in which the dextrose tolerance of certain representatives was found to be 10 g. per kilo. In this animal, on August 17, injection of 1 g. Kahlbaum levulose led to a "moderate" reduction-test in the urine. The tolerance was therefore less than 1 g. per kilo.

Cat 18 (weight 2300 g.) on June 21 received a subcutaneous injection of 6 g. levulose, and on the next day an injection of 20 g. levulose. There was heavy levulosuria, and after the second injection, which was more than 8 g. per kilo, the levulosuria continued for about 24 hours.

Cat 53 (weight 4½ kilos) on November 11 assimilated perfectly a subcutaneous injection of 1 g. levulose. On November 14, an injection of 2 g. levulose caused a definite trace of reduction to appear in the urine. On December 1 a subcutaneous injection of 10 g. dextrose was completely assimilated. The normal weight of this cat was not less than 4½ kilos. The tolerance for levulose was therefore less than 0.44 g. per kilo, as compared with the 3 or 4 g. dextrose per kilo normal for cats.

Cat 26. On September 16, subcutaneous injection of 3 g. levulose (about 2 g. per kilo) caused a levulosuria of 1.2 per cent, with excretion of 0.78 g. After injection of 2 g. on September 19, there was a pronounced reaction in the urine. The same dose was repeated on September 22, with a resulting excretion of 0.86 per cent or 0.456 g. On September 24, injection of 1 g.

levulose gave a definitely positive reaction in the urine. Likewise the injection of ½ g., on September 26 and again on September 28, was followed by a distinct reduction-test in the urine; in one of these cases the solution was 80 per cent, in the other case 10 per cent; the concentration of solution as usual had no effect upon the assimilation. Placing the "normal" weight of this cat at the low figure of 1½ kilos, the levulose tolerance subcutaneously is scarcely 0.3 g. per kilo, or a tenth of the dextrose tolerance.

Dog 21 received subcutaneous levulose injections which may be tabulated as follows. The tolerance proved to be less than 1 g. per kilo, presumably not more than a tenth of the dextrose tolerance. The figures in the per cent column represent not a percentage of the dose injected, but the concentration of levulose in the urine-specimens.

	Injection		Excretion		
Date	G. by Weight	G. per kilo	Percent	Grams	Duration in hours
Apr. 30	6.83	1	0.43	0.63	About 7
May 3	13.6	2	0.36	0.61	" 7
" 7	20.22	3	0.45	0.468	
			1.95	0.39	" 7
				Total 0.858	
" 10	27.58	4	0.62	0.868	Less than
			4.96	1.091	24
				Total 1.96	
" 20	34.4	5	1.59	1.272	
			5.2	0.468	About 24
			0.28	0.812	
				Total 2.552	

Concerning the peculiar physiological behavior of levulose, the following remarks seem indicated.

The tolerance as established by different channels of administration is widely different. By the intravenous method, authors found the saturation limit equal to or greater than that of dextrose. By oral administration, the tolerance of levulose is slightly less than for dextrose (or, according to some authors — especially Hohlweg and De Filippi in the dog — markedly less). By the subcutaneous method, the assimilation limit of levulose is surprisingly low. The wide differences may be explained hypothetically as follows. (1) By intravenous administration, all that is learned is the amount of sugar which the blood and tissue-fluids will immediately bind and hold without the occurrence of an overflow through the kidneys. As Blumenthal says, a tiny amount above this "saturation limit" (properly so named) suffices

for mellituria. This method determines nothing concerning the readiness with which the tissues withdraw sugar from the blood. The levulose in this instance is free to circulate and re-circulate, till finally all is picked up from the blood by the liver or tissues. (2) After oral administration, the liver presumably stops most of the levulose, and with ordinary doses little or none of it reaches the general circulation. (3) After subcutaneous administration, the levulose is absorbed directly into the systemic vessels. There is a continuous absorption from the area of injection. Therefore, in order to prevent an excess from accumulating in the blood and overflowing the kidneys, this method demands that the tissues actively remove the levulose from the blood at a definite rate. Their very limited ability to meet this demand is proved by the ease with which subcutaneously injected levulose appears in the urine.

This observation agrees with that of De Filippi concerning the lowering of the levulose tolerance as a result of the Eck fistula in dogs. Both support the view of the importance of the liver for the assimilation of levulose, and give a theoretical basis for the levulose test of hepatic function. Possible fallacies of the levulose test for this purpose may be the following. (1) According to Voit's injection-experiments on human beings, it may require a reception of 20 to 30 g. levulose into the general circulation before appreciable levulosuria results. (2) Portal stasis in some liver-diseases may delay absorption of the levulose from the intestine, thus giving the liver more time for its work and masking its impaired function. The experiments of Wehrle are analogous. (3) Disease or impaired function of the liver in other respects may not necessarily reduce greatly its power to warehouse levulose. (4) Abnormal portal anastomoses may permit absorption of part of the levulose directly into the systemic circulation. (5) Infection or intoxication may result in impaired assimilative functions of the liver or other organs, in cases which are not specifically liver disease.

Levulose to some extent fulfills the conditions imagined for dextrose by those who devised the thoracic-duct hypothesis of alimentary glycosuria. That is, comparatively small quantities of levulose reaching the general circulation very readily give rise to mellituria. The difference between the tolerance of dextrose by mouth and levulose by mouth would permit some interesting deductions concerning what proportion of sugar is stopped by the

liver and what proportion is allowed to pass through it to the general circulation, if only we knew whether dextrose, levulose and other sugars are picked up with equal avidity by the liver. The existence of such an equality is doubtful.

Levulose obeys the paradoxical law to a greater degree than any other sugar. The apparent tolerance of levulose is a small fraction of a gram per kilo. The real tolerance is practically as high as that of dextrose. On this point, comparison with galactose [see next section] is instructive. Subcutaneous injection of 1 g. per kilo of either levulose or galactose causes a very similar degree of mellituria. But as the quantities of injected galactose increase, the excretion rises very markedly. With levulose, the excretion remains insignificant. Still more notable is the comparison between levulose and maltose. It was noted that the urine remained sugar-free after subcutaneous injection of 1 g. maltose per kilo. The apparent tolerance for maltose is thus three or four times as great as that of levulose. But as the doses increase, maltose begins to exhibit the difficult assimilation proper to it as a disaccharide. The amount excreted soon becomes greater than that following an equal dose of levulose. After injection of 90.56 g. maltose in a dog, Hohlweg witnessed an excretion as high as 33.92 g. There is no possible dose of levulose subcutaneously which could cause the excretion of anywhere near one-third of the quantity injected. Thus, with different doses, the ratio of excretion of different sugars is different. The reason for this behavior might be an interesting inquiry. Levulose does not appear in the urine so easily because the kidneys are unduly permeable for it; on the contrary the Blumenthal saturation-test shows equality with dextrose. To some extent the tissues apparently utilize levulose more slowly than dextrose, and perhaps also an undue proportion of the levulose entering the systemic vessels must be removed by the liver. Yet the process is not excessively slow, for the excretion-time of even a large dose of levulose is not very great. The above conditions do not fully explain the readiness of excretion of part of the smallest doses of levulose, and the readiness of assimilation of most of even the largest doses. There would appear to be a different assimilation-curve of each sugar in proportion to its concentration in the blood; and that of levulose might be supposed to start very low and rise very steeply. The known facts are expressed by saying that all sugars obey the paradoxical law, but some obey it to a greater degree than others.

6. Galactose.

Galactose is the least easily assimilable of the common hexoses. It is characterized also by the lowest oral tolerance of all the ordinary sugars, the limit being placed by von Noorden at 20 g., as compared with 150–180 g. dextrose. The important changes resulting from slower absorption are well illustrated here; for the assimilation limit of lactose is given by von Noorden as about 120 g., and this must be assimilated in the form of dextrose and galactose. Galactose is, in general, a more difficultly fermentable sugar than dextrose or levulose. It is reckoned among the true glycogen-formers, on the basis of various feeding experiments in glycogen-free animals, and of the direct perfusion experiments of Grube (3) with tortoise-livers. McGuigan found it to be capable of direct oxidation by the surviving muscles and liver.

The liver has been assigned a specific rôle in the assimilation of galactose, as of levulose. Alimentary galactosuria has been proposed as a test of the hepatic function; a demonstrable lowering of the tolerance has been claimed in cases of liver disease. The literature is given in the recent paper of Hirose, who finds alimentary galactosuria commonest in cirrhosis and catarrhal icterus, less frequent in other liver troubles. It may also be found in those classes of patients with a tendency to alimentary glycosuria, in particular hyperthyroidism; it is less evident in neurasthenia. Pollitzer finds that alimentary galactosuria may occur in patients with symptoms of disease of the visceral nervous system. It probably depends on a disturbance of the galactose-fixing power of the liver; but he considers all sugar-tests unreliable, especially in cases of portal hypertension.

The analyses by Pavy (3) show the distribution, utilization, and excretion of galactose after intravenous injection. In other experiments Pavy injected 1 g. galactose per kilo subcutaneously in rabbits; they were killed after two hours, and the urine contained 13 to 24 per cent of the injected dose.

Blumenthal found that in a rabbit whose intravenous saturation limit for dextrose was 2.6 g., that for galactose was 0.5–0.6 g. In another rabbit the limit for dextrose was 2 g., and for galactose 0.4–0.5 g.

McGuigan, injecting intravenously 0.5 per cent sugar-solutions at a rate of 1 cc. per minute, found that sugar appeared in the urine after injection of 60 cc. galactose solution, as compared with 40 cc. of dextrose solution.

Fritz Voit presented the following table of his subcutaneous injections of galactose in human patients.

Injected g.	Excreted g.	Duration of Excretion in hours
9.23	0.16	1
9.58	Trace	4½
29.43	Trace	5½
30.26	Trace	3½

Rosenberger (p. 11) tabulates other subcutaneous injections in human patients as follows.

Injection g.	Excretion g.	Authors
5	0	Achard & Weil
9.229	0.159	" " "
20	0.6	H. Strauss
26	0.8	"
28	0.8	"

The following table contains the results of Hohlweg and Voit with subcutaneous galactose injections in rabbits.

Injected g.	Excreted		Duration of Excretion in hours
	g.	%	
At room-temperature:			
8.886	1.056	11.89	11½
19.84	6.216	31.33	24
With over-heating:			
8.886	0.568	6.39	11½
19.840	1.526	7.69	22½
9.	0.716	8.	22

Hohlweg presents the following table of results from subcutaneous galactose injections in a dog.

Injected g.	Excreted		Duration of Excretion in hours
	g.	%	
At rest:			
88.	28.04	31.86	24
88.	25.2	28.65	24
With work in treadmill:			
88.	9.862	11.2	24
88.	9.536	10.83	24

The subcutaneous galactose tolerance in experimental animals seems never to have been investigated. My experiments with Dog 21 may be tabulated as follows.

Date	Injected		Excreted	
	g. absolute	g. per kilo	% in Urine	g.
May 24	7	1	0.65 0.24	1.3 0.06 Total 1.36
May 27	21	3	1.2 7.3	2.22 1.46 Total 3.68

The tolerance in the dog is therefore less than 1 g. per kilo. It may again be noted that though the "apparent" tolerance of galactose subcutaneously approaches that of levulose, increase of the dose quickly proves that galactose obeys the paradoxical law to less degree than levulose. Nevertheless, a galactose paradox is well marked, as reference to the tables of Hohlweg and Voit will show. As with the other sugars, the absolute quantity of galactose that can be burned is limited only by the quantity the animal can receive without fatal result.

7. Glycogen.

To mention this substance is to think of Bernard and Pflüger. The former discovered it and established the doctrine concerning it. The latter devoted much of his life to it, perfected the methods of analysis, and applied them to the study of carbohydrate metabolism and to the correction of numerous conclusions of other investigators. Pflüger's book contains the world-knowledge of the subject up to 1905. His last word on analytic methods was his paper (25) in 1909. Much yet remains to be determined concerning the biological status of glycogen. Pavy and Seegen [see Pavy's books, and Seegen (2)] have long contested the prevalent views on the subject. The question concerning glycogen lies essentially between two opinions; whether it is a simple reserve as Bernard believed, or whether it is a substance of intrinsic importance to the cell. A few of the numerous investigations may be briefly mentioned.

Claude Bernard taught that the liver in earlier fetal life contains no glycogen. The analyses by Pflüger (3 and 4) of early fetal livers of various domestic animals revealed the presence of glycogen in quantities from mere traces up to 0.79 per cent, gen-

erally no more than 0.1 per cent. His conclusion was that there is no ground for the assumption that early fetal livers contain no glycogen; and he left undecided the question whether such livers are essentially and normally poorer in glycogen than the post-fetal liver, or whether the low content in his analyses was due to impaired nutrition of the animals. Mendel and Leavenworth have given a more definitive answer to this question, and one more in accord with the views of Bernard. A fuller review of the literature is given by them. They failed to find glycogen in measurable quantity in the livers of embryo pigs of 85–230 mm. They also tested other embryonic organs, and came to the general conclusion that glycogen is a store of nutrient energy rather than a peculiar mark of histogenesis.

Young or rapidly growing tissues are generally glycogen-rich. Tumor-cells may contain glycogen even when the tissue from which they arise contains none (Askanazy).

Pflüger's view, like that of the world in general, was originally that in starving animals, the amount of glycogen steadily diminishes from the beginning of starvation to death. Rolly called attention to Pflüger's opinion [as presented in Pflügers Archiv, Vol. 76, p. 11] and also to earlier analyses by Külz, which showed an increase of glycogen in starving rabbits, though Külz had not grasped the significance of his figures. Rolly proceeded to make rabbits glycogen-free by fasting and strychnin, and then prolonged the fast still further. He found that under these conditions, they reaccumulate glycogen to replace that which was lost. This glycogen is formed from the body-protein, and the increased destruction of protein for the purpose of forming glycogen is indicated by an increased nitrogen-excretion. Rolly concluded that since a starving animal possesses glycogen practically to the end, the probability is that glycogen is continually being used during starvation, and continually reformed from the body protein. Pflüger and Junkersdorff [see Pflüger (7)] then published experiments to the same effect, the procedure employed being as follows. A dog fasts 10 days, and each morning of the last 3 days receives one gram phloridzin subcutaneously. If killed 7 hours after the last injection, he is found practically glycogen-free. If not killed till 24 hours after the last injection, some reaccumulation of glycogen is found to have occurred. Pflüger (17) proved by analyses, which were an elaboration of Claude Bernard's original work, that a well-marked increase of glycogen occurs during the

all-winter fast of dormant frogs. Artificial heat causes the glycogen to disappear, just as summer heat does. Pflüger (14) showed that also in the higher animals, on complete starvation, the liver continues to form glycogen to the day of death. If either pure fat or pure albumin is supplied as food, the glycogen-formation either ceases or is reduced to a minimum. If an excess of pure dextrose is given, the glycogen-formation is greatly increased. Pollak (1) proved that fasting rabbits, made glycogen-free by strychnin, can by small increasing doses of adrenalin be made to store liver-glycogen in a quantity only equalled in carbohydrate-fed animals. But the muscles remain entirely or almost devoid of glycogen.

After some debate, it seems established that glycogen exists in the living cell, that it is not an artifact nor a postmortem product. It lies embedded in the protoplasm in the form of amorphous masses; it is generally supposed to be united with a binding-substance (Trägersubstanz), perhaps of protein nature. All glycogen may not be identical. Naunyn [ref. by Pflüger (1), p. 372] observed that in chickens, muscle-glycogen is colored violet by iodin, liver-glycogen reddish-brown. Bernard [(3), p. 553] found that paralyzed muscles load themselves with glycogen which with iodin gives a pure blue color like starch. Tebb distinguished different steps in the hydrolysis of glycogen, which she distinguished as soluble glycogen, erythrodextrin, and achroödextrin. The question is still undecided whether glycogen is a way-station on the road to fat, or whether dextrose is synthesized into fat by a way which does not lie through glycogen. It has been reported that fat-tissue contains glycogen only so long as fat-formation is in progress. Frank and Isaac (3 and 4) have assigned considerable speculative importance to glycogen. As opposed to the common view that glycogen is broken down into dextrose to be burned, some have suggested that the cell burns carbohydrate in the form of glycogen. A discussion is given by Pflüger [(1), beginning p. 211]. Embden and Kraus, with liver-perfusion experiments, found evidence suggestive of the consumption of glycogen as such by the liver. Reference has previously been made to the work of McGuigan, showing consumption of sugar by surviving muscles after cessation of glycogen-formation, which consumption was increased by stimulation of the muscles. Lately Gayda, with the method of perfusion of the isolated [rabbit] heart used by a number of previous writers, has found a certain utilization of glucose but very little loss of glycogen.

Stewart has demonstrated glucose consumption by the isolated human heart. Camis has formed the opinion that the heart muscle of herbivoræ burns glucose, while that of carnivoræ burns only glycogen. Jensen started from the well-established fact that the heart retains practically normal glycogen values at a period of starvation when the skeletal muscles are reduced to $\frac{1}{10}$ to $\frac{1}{30}$ their normal quantity. But by starving animals to the point of death, Jensen proved that the heart can still beat when glycogen is completely absent. Knowlton and Starling have given the most recent proof of the utilization of dextrose by the dog-heart in perfusion experiments.

Theories concerning glycogen and theories concerning diabetes have been closely interwoven. Diminution of the glycogen of liver and muscles is the rule in severe diabetes, but complete absence of glycogen probably never occurs even in totally depancreatized dogs, except as a terminal condition. In contrast to this depletion of the normal reservoirs, there may be the abnormal occurrence of glycogen in other places, especially (*a*) nervous system, (*b*) liver-nuclei, (*c*) blood, (*d*) kidneys and urine. The earlier literature is given by Pflüger [(1), p. 445], who suggests the glycogen-content of the plasma as the cause of the deposits elsewhere.

(*a*) *Nervous System.* — According to Pflüger, the normal brain is almost but not absolutely glycogen-free. The pathological distribution has been studied by Neubert. He found glycogen normally present in the hypophysis, but increased in quantity in diabetes. Microscopically demonstrable glycogen occurs physiologically in the central nervous system only in fetal life. In diabetes, glycogen may be demonstrated both in the brain and spinal cord. But similar deposits may be found in miliary tuberculosis, carcinoma and other cachectic states. Mironesco's findings were similar. Neubert interpreted the condition as a tendency of injured cells to revert from a specialized to a more primitive metabolism.

(*b*) *Liver-nuclei.* — Ehrlich in 1883 described and pictured glycogen in diabetic liver nuclei. The nuclear glycogen has been studied more particularly by Huebschmann and by Klestadt. They found it not only in diabetic but also in some non-diabetic livers. Klestadt defined its presence under the following conditions; (1) rich carbohydrate feeding (in rabbits), (2) disturbance of carbohydrate metabolism (diabetes), (3) circulatory disturb-

ances, (4) infectious and toxic conditions. O. Rosenberg showed the phenomenon to be without specific significance, asserting that the glycogen in diabetic livers cannot be distinguished microscopically from the normal as respects quantity, site or other characteristics. He found the nuclear glycogen to be merely a consequence of œdema, which brings the glycogen into solution and allows it to pass through the nuclear membrane. He could demonstrate it in the liver in all cases of circulatory stasis, especially heart and lung troubles, and almost constantly in pulmonary tuberculosis. This view seems opposed to the findings of Askanazy and Huebschmann, that the swollen nucleus may contain glycogen when the cytoplasm contains none.

(*c*) *Blood.* — An abnormal richness of the blood in glycogen may be found in diabetes. Ehrlich in 1883 demonstrated glycogen in diabetic plasma. Gabritchewsky in 1891 found it increased in the leukocytes and present in the plasma of human diabetics and depancreatized dogs. He, also others, have considered that the plasma-glycogen is derived from broken-down leukocytes. He also found increase of the glycogen after dextrose injections, but not after rich carbohydrate feeding; it was absent in phloridzin glycosuria; he concluded that the leukocytes form glycogen from the blood-sugar in hyperglycemia. But he also found increase of glycogen in various infections or cachectic diseases, and after peptone injections in animals. Kaufmann [ref. by Pflüger (1)] also demonstrated glycogen in diabetic plasma. Minkowski [(1), p. 100] found a higher glycogen-content in the pus of diabetic dogs than in that of normal or phloridzinized animals.

(*d*) *Kidneys and Urine.* — Armanni [ref. in texts] recognized a peculiar clear and swollen, cystic appearance of the cells of the tubuli recti and the descending limb of Henle's loops of diabetic kidneys. Ebstein (1 and 2) made a similar observation. Ehrlich discovered that the appearance in question is due to a filling of the cells with glycogen, and the presence of glycogen was confirmed by Straus. Policard and Garnier found after large doses of phloridzin in white rats, a "vitreous" degeneration which was limited strictly to cells of the convoluted tubules, and which they regard as characteristic. They appear not to have tested for glycogen. Süssenguth (1) found that in the glycogen-loaded renal cells, the nuclei also contain glycogen; and he referred to an earlier brief note to the same effect by Best. Leube is credited with being the discoverer of glycogen in the urine in some cases

of diabetes. Simon studied the matter more carefully, and considered the presence of glycogen as a sign of glycogenic degeneration of the kidney. Falta and co-workers are said to have observed that injection of dextrose in depancreatized dogs produces along with increased glycosuria an excretion also of glycogen.

There are three hypotheses seeking to explain the glycogen deposits mentioned. The oldest one is that the leukocytes, the renal cells, and possibly other structures fill themselves with glycogen which they synthesize from the sugar of the blood or urine. The second is, that since glycogen has been proved to exist in diabetic blood-plasma and diabetic urine, the cells in question merely pick up this preformed glycogen from the fluid surrounding them. Loeschke in particular has attempted the formal proof of this view. The reverse of his opinion is that of Simon, who regards the finding of glycogen in the urine as evidence of the existence of a glycogenic degeneration. The third hypothesis is that the glycogen represents a reaction to irritation. Lepine [(1), p. 488] presents evidence that if a ten per cent salt solution is injected under an animal's conjunctiva, the retina becomes infiltrated with glycogen. Others have compared the glycogen-laden leukocytes of diabetes with those of infected areas, and suggest that this peculiarity of the white blood-cells both in depancreatized dogs and in many human diabetics may indicate merely a focus of infection somewhere in the body.

A more complete experimental answer to these questions seems desirable, and the opportunity is apparently afforded by parenteral injections of dextrose, glycogen, and dextrin. It is safe to infer that the various deposits have not always the same significance; it is noteworthy that all of them have been found in conditions other than diabetes or hyperglycemia. At present the evidence warrants the belief that hyperglycemia is at least one factor; among such evidence may be mentioned the following: (1) Gabritchewsky's increase of leukocytic glycogen by dextrose injections. (2) Minkowski's observation that the pus of diabetic dogs contains more glycogen than the pus of non-diabetic dogs. (3) The finding of Nishi (3) that the normal rabbit kidney contains no glycogen; in hyperglycemia without glycosuria it contains a trace; in hyperglycemia with glycosuria it contains a small quantity. Nishi's work was especially with adrenalin. In a fasting, dextrose-injected cat (Cat 171) in which the liver and muscles were glycogen-rich, I found no trace of glycogen in the kidneys.

Some of the earliest work with glycogen injections will be treated under diastases. For the present purpose we may begin with Pavy. He found, confirming others, that intravenous injections of glycogen cause an increase in the blood-sugar, and, in case of larger doses, glycosuria. Pavy (3) further reported intravenous glycogen injections of 1 g. per kilo, which caused hemoglobinuria and the appearance of dextrose and dextrin in the urine. Schiff, on the contrary, denied the occurrence of either glycosuria or increased blood-sugar after glycogen injections. Tieffenbach concluded that glycosuria is unusual, and results only from large doses. He found no glycogen in the urine. Tiegel frequently observed glycosuria after injections of glycogen.

The above references are mostly taken from the paper by Boehm and Hoffmann, in 1877. These authors used cats, and injected 3 to 10 g. glycogen into the jugular vein, the injection being delivered very slowly, so that several hours were required. Polyuria [due to contained salts ?] and hemoglobinuria were observed. Sugar was present in the urine, but the polariscope indicated four times as much as the Fehling test. By several precipitations with alcohol, they purified a substance from the urine, which they identified as achroödextrin. Its dextrorotatory power was about four times that of dextrose. On boiling with a mineral acid, it was converted completely into dextrose. Animals were bled to death an hour after ending the injection. Dextrin was found in the blood thus obtained. No glycogen could be found in either blood or urine. The liver contained both glycogen and dextrin. The authors note that the dextrin could be partly precipitated by adding to the urine 2 or 3 times its volume of 95 per cent alcohol; but most of the dextrin required 6 or 8 volumes of alcohol to bring it down. They remark that the process of break-down seems to resemble that in digestion. The same authors (3) also found that cats exposed to cold are able to utilize intravenously injected glycogen even up to the time of death.

Teissier and Zaky made repeated intravenous injections of glycogen into rabbits, the highest dosage being 1–1½ g. per kilo. The animals lost flesh. At autopsy the livers were found congested. The urine showed deeper color, diminished quantity, and diminished total nitrogen after an injection, but the normal values promptly returned. Dextrose was found in the urine only once. Other abnormal constituents were generally absent. The urine never contained glycogen.

The work of Wassermann and Citron concerning the production of a glycogen-amboceptor by means of glycogen injections will be considered in Section 12.

Pavy (3) had refrained from subcutaneous injections of glycogen, because under such conditions, "glycogen with the colloidal property it possesses could scarcely be expected to reach the circulation as such." Fritz Voit made one subcutaneous injection of 10 g. glycogen in 100 cc. water in a fifteen-year-old boy. No carbohydrate appeared in the urine. Voit's result is beyond question, because he not only tested the urine for sugar and glycogen, but also boiled with HCl and tested again for sugar, always with negative result.

Mendel and Mitchell injected glycogen subcutaneously and intraperitoneally in rabbits and dogs, in doses of 2.1 to 4.6 g., and a dose of 1.74 g. in a cat. The urine never contained sugar, but always achroödextrin in quantities from 0.1 g. to 0.68 g.

The publication of Teissier, Sarvonat and Rebattu brings glycogen-glycosuria into relation with phloridzin glycosuria. Another paper, by Teissier and Rebattu, is to similar effect. In using phloridzin as a test of renal function, they found absence of glycosuria in a number of tubercular patients, in whom there was no trace of albuminuria during life nor any sign of abnormality of the kidney at death. But in such patients, the liver was always found fatty or cirrhotic. The authors therefore assumed that the normal glycogenic function of the liver is somehow necessary for phloridzin glycosuria, and so they tried glycogen injections. They found that 0.05 g. (!) of glycogen given subcutaneously simultaneously with the phloridzin brought out the glycosuria in such cases. They say that glycogen alone in "minimal doses" will cause glycosuria, but the glycosuria is greater when given with phloridzin (in patients refractory to phloridzin alone).

It is interesting to compare the glycosuria observed by Teissier and Rebattu from "minimal doses" of glycogen, with the complete absence reported by Voit from 10 g.; also to compare the dextrinuria witnessed by Mendel and Mitchell from small doses of glycogen in animals, with the completely negative findings by Voit in man.

Comparisons between the effects of glycogen and dextrin have been made. Leube and Gürber claimed that dextrin is quantitatively excreted, while the same amounts of glycogen are completely assimilated. P. Mayer (1) reported large excretion

of achroödextrin after injections of erythrodextrin, but injections of glycogen as high as 5 g. were retained completely.

The largest injections of glycogen ever made are those of Fichtenmayer. The results, as tabulated by him, are reproduced in Chapter IV. The quantities injected ranged from 5 to 40 g., in rabbits weighing 1½ to 2 kilos. With 9 injections, there were only four sugar-reactions in the urine. Possibly dextrin was present; no tests are mentioned. Fichtenmayer gained the impression that the glycogen was broken down locally, but the comparatively large dextrin excretion after Mendel and Mitchell's small doses shows that this is not the whole explanation.

From one point of view, it seems strange that glycogen, a colloid, a substance native to the body, and an important element in metabolism, should be tolerated so poorly when injected. Its effect upon the organism is slightly but definitely toxic, more so than the effect of any sugar. The organism attacks the injected glycogen with its utmost power, breaking it down into dextrin and sugar, and excreting a portion unused. This fact would appear as a further indication that the carbohydrate stores of the liver must be transported to the tissues in the form of sugar, or at least not in the form of glycogen or dextrin. No positive conclusion can be drawn, since it is not certain that the artificially isolated glycogen is in all respects identical with the natural substance. Inasmuch as I intended to try the effects of glycogen injections in diabetes [see Chapter XVIII], it became of interest to know whether the behavior of injected glycogen may be different according to its source or its mode of preparation. A series of experiments in this direction led me to the following conclusions.

1. As tested by subcutaneous injection, there is no difference of behavior between liver-glycogen and muscle-glycogen.

2. As tested by subcutaneous injection, there is no difference between glycogen of the same species and that from a different species.

3. As tested by subcutaneous injection, there is no difference between glycogen prepared by boiling out without the use of alkali, or by boiling with weak or with strong alkali.

In other respects, the proposed series of glycogen experiments was left unfinished. Dog 66 (weight 13 kilos) on July 20 and 21 received subcutaneous glycogen injections of 1 g. and 2 g. respectively. The urine remained negative for both sugar and dextrin. The attempt to determine the glycogen tolerance was broken off

at this point. A double standard may be required in such a case: the dose at which dextrin begins to appear in the urine, and the dose at which sugar begins to appear in the urine. The above findings agree with the statement of Teissier and co-workers, that dogs do not show glycosuria after the minimal doses which are asserted to cause it in human beings.

In several rats and guinea-pigs after relatively large subcutaneous injections of glycogen the urine was found heavy with reducing sugar and a non-reducing achroödextrin. Kitten 12, weighing 318 to 360 g., in six days received 5 injections of respectively 10, 20, and 30 cc. of 10 per cent glycogen solution. The urine was examined only after the last injection; it showed the presence of reducing sugar, dextrin, and albumin. Rat 6, weighing about 150 g., received glycogen injections daily for the month August 2 to September 2. The doses were mostly 2 cc. 10 per cent glycogen solution at first, later 4 cc. For the sake of warmth and comfort the rat was left in the general cage with other rats. Specimens of urine collected every few days showed sugar and dextrin, but these promptly disappeared when the injections were omitted. Neither increase nor diminution of utilization was apparent. Like Teissier and Zaky's rabbits, this rat lost weight, the loss in a month being about 25 g. or $16\frac{2}{3}$ per cent. No other symptoms were visible, and the animal remained lively.

The reports in the literature concerning doses of different sizes indicate that there is a glycogen paradox. Utilization can be increased at will merely by increasing the dose.

8. Dextrin.

Dextrins occur normally in liver, muscles, and other locations, probably as intermediate stages in the glycogen economy. Mention has already been made of the dextrins found by Tebb in the hydrolysis of glycogen in vitro, the dextrin isolated by Pavy from the liver, the presence of dextrin in normal urine as demonstrated by Baisch and others, its increase in diabetic urine according to the analyses of von Alfthan, von Noorden, and others, etc. In the organs, erythrodextrin either is present in small quantity or is confused with glycogen, for no record concerning it is found the dextrin referred to in the organs, blood, and urine is always achroödextrin. Seegen (1) found in the liver a dextrin-like substance, which in most of his analyses was equal to about half the amount of glycogen present. It was non-reducing, and completely

precipitated only by 90 per cent alcohol or stronger. Most of it was not brought down with the glycogen by the Brücke-Külz method.

Under normal conditions the passage of higher dextrins through the kidney is impossible. The only exception may be the sudden injection of an enormous dose intravenously. For this reason, all the more interest is due to two reports of the presence of large quantities of these substances in the urine. One is that of Yashiro Kotake, who found a considerable quantity of erythrodextrin in the urine of a dog under unknown conditions. This author mentions that E. Reichert found dextrin repeatedly in diabetic urines, and that Leube found such a substance in the urine of two diabetics and described it as glycogen. [But the dextrin reported by others in diabetic urine is always achroödextrin.] The other report is that of Hirsch (2), who, in a series of pan-thyroidectomized dogs, found in two cases that amylodextrin fed in small quantities by mouth was excreted unchanged in the urine. In one of the cases, after feeding of 20 g. amylodextrin, there was elimination of 3 g. of the unchanged dextrin in the urine. As heretofore remarked, the assimilation-limits of the different dextrins have never been determined, and it is not certain that limits may not normally exist. But the excretion of such a quantity of unchanged amylodextrin implies such extensive abnormalities of digestion and absorption, of renal activity, and probably of tissue-functions, that we can only express our present complete ignorance of the subject. It is analogous to the paralysis of dextrose-utilization observed by Underhill and Saiki in such animals.

Fritz Voit included several dextrins in the long list of carbohydrate substances used for subcutaneous injection in human subjects. He tested dextrins prepared both by acid and by diastase; no difference in the effects appeared. His results in tabulated form are as follows.

	Injection	Excretion			
	g.	g.	%	In form of	Duration in hours
Erythrodextrin	14.57	2.03	14	Achroodextrin	19½
Achroodextrin	10.37	3.49	34	"	16
	10.21	2.48	24	"	13½

Von Leube and Gürber are said to have found that in animal experiments dextrin given subcutaneously is readily absorbed but appears unchanged in the urine. Under similar conditions, 15 per cent solutions of glycogen were assimilated without appear-

ance of any appreciable amount of carbohydrate substance in the urine.

P. Mayer (1) reported that when doses of 10 g. erythrodextrin are injected subcutaneously in rabbits, 34 to 50 per cent of the amount can be recovered in the urine in the form of achroödextrin. Twice the dose can be given by mouth without appearance of a trace of carbohydrate in the urine. After subcutaneous injections of 5 g. glycogen, the urine of the rabbits remained free from carbohydrate. Mayer discusses on this basis some of the theoretical questions concerning the utilization of glycogen; whether it is normally consumed as such or converted into sugar, and why glycogen should behave differently from the dextrins presumably formed from it.

Mendel and Mitchell made subcutaneous injections of dextrin in 2 rabbits and 2 cats. The injected substance was a mixture of dextrins prepared by the action of saliva upon starch. The doses ranged from 2 to 3.5 g. No glycosuria resulted. The amount of achroödextrin excreted varied from 0.22 g. to 0.88 g. The authors could observe no special difference between the effects of dextrin and those of glycogen.

I have made a number of dextrin injections in rats and guinea-pigs, as controls to the glycogen injections. The preparation used was bought from Eimer and Amend; it is labelled "C. P. Dextrin," and gives an erythrodextrin color with iodin and no reduction with copper. The effects have been identical in all respects with those of glycogen. There is the same glycosuria, the same excretion of achroödextrin, the same slow emaciation without other symptoms in consequence of prolonged daily administration. Only one large injection has been given in a dog. This was Dog 34 on April 7. The animal, weighing 6400 g., received a subcutaneous injection of 50 g. dextrin. The excretion of reducing sugar and achroödextrin continued for a little more than 24 hours.

In most species, therefore (rat, guinea-pig, dog, presumably others. Possibly the rabbit is an exception.), large subcutaneous injections of dextrin cause excretion of reducing sugar and achroödextrin. The presence or absence of mellituria is merely a matter of dosage. It is evident that a dextrin paradox exists. It may also be remarked incidentally, that, though glycogen is frequently classified with starch, and is called "animal starch," "zoöamylum," etc., by the test of subcutaneous injection the behavior of glycogen resembles that of erythrodextrin more closely than it does that of starch.

9. Starch.

As has been stated heretofore, in health the assimilation of starch by mouth is unlimited. Strauss and von Noorden have reported glycosuria *ex amylo* in fever patients and alcoholics. Hofmeister (2), after sufficiently prolonged starvation in dogs, observed glycosuria as a result of starch feeding, the amount necessary being generally about 5 g. per kilo. Glycosuria *ex amylo* is therefore not an absolute test of diabetes. The relationship is merely quantitative. It so happens that the digestion and absorption of starch are sufficiently slow that the organism can nearly always metabolize the resulting sugar perfectly. But glycosuria may follow starch ingestion whenever the carbohydrate economy is sufficiently deranged, whether the derangement is of diabetic nature or of some entirely different character.

Hirsch (1) claimed that after ingestion of raw starch, starch-grains can be found in the urine. When cooked starch is ingested, the excreted grains show the characteristic swelling. That is, the grains must be absorbed as such through the bowel wall, must circulate in the blood, and must pass through the epithelium of the kidney, all the time retaining their character as starch-grains. Wile found starch in the urine of starch-fed, not of milk-fed, children. Verzar (3) confirmed the report of Hirsch. Both used the most scrupulous care in their methods, cleansing all utensils chemically and passing them through the flame, etc. But Voigt repeated the work, called attention to the multitude of sources from which contamination with starch-grains is possible, and reported his experiments negative. Probability is on the side of Voigt.

Fritz Voit injected amylodextrin (soluble starch) subcutaneously in human patients. His results are tabulated by him as follows.

Injection	Excretion			
g.	g.	%	In form of	Duration hours
5.78	0.84	15	Achroodextrin	33
11.58	3.20	28	"	10 1/2
11.57	1.21	10	"	46 1/2

Mendel and Mitchell injected $2\frac{1}{2}$ g. soluble starch into the peritoneum of a rabbit, and recovered 0.76 g. in the urine. They injected 6.4 g. intraperitoneally in a dog; the excretion lasted

15 hours and amounted to 0.43 g. The dextrin-like substance recovered gave a purple-blue reaction with iodin, no reduction test prior to hydrolysis, and a dextrorotation of 174.6 degrees. The authors conclude that it represents the injected starch, altered only slightly if at all. Mendel, in a brief further report, states that soluble starch injected parenterally reappears in the form of dextrin-like compounds. Utilization (or retention) is greatest after subcutaneous injection, less after intraperitoneal, least after intravenous. Tissue amylases apparently play some part. A complete utilization, such as claimed by Moscati for starch, was never observed.

The mention of Moscati brings up a group of intravenous injection experiments which, for the sake of unity, have been reserved for consideration together. Moscati injected dogs with starch subcutaneously and intravenously. The doses were from 1 to 3.9 g. per kilo, and represented sometimes an injection of 300 to 450 cc. of starch solution into the jugular vein. He tested the urine, saliva, pancreatic juice, bile, and intestinal contents for both starch and sugar, with findings invariably negative. Most of the experiments were performed on animals which by fasting had been rendered relatively glycogen-free. In these animals Moscati claimed to be able to prove that the starch was taken up by the organs of the body, especially the liver, spleen, lungs, and muscles; that it could be demonstrated in them for a number of days following the injection, side by side with glycogen; and that the amount of starch gradually diminished while that of glycogen gradually increased, so as to lead to the inference that the starch is transformed directly into glycogen, without the mediation of sugar. The pancreas and the brain remained free from starch (and glycogen). The transformation of starch into glycogen occurred more quickly in the muscles than in the liver. That such a change can be brought about, and especially that it can take place in the muscles, is of course a discovery of far-reaching importance, if it can be confirmed. The high tolerance for starch, none of the large quantity injected being excreted either as sugar or as starch, is another remarkable claim. The following observations of Moscati have a bearing upon the subject of diastases. First, he found that traces of starch still remained in the blood 8 or 10 days after the starch injection, evidently a transport or a leakage from the organs which still contained starch. Second, he injected two depancreatized dogs with

starch. Even in the one which received a 300 cc. intravenous injection, containing 8 g. starch, the glycosuria remained unchanged. The organs contained only traces of glycogen. The spleen and the liver contained small quantities of starch. What became of the rest is uncertain. Third, whereas starch could remain unchanged in the liver of the living animal for considerably more than a week, an excised piece of liver placed in the incubator became starch-free within a few hours.

Moscati's publication drew the fire of De Filippi (2), whose criticisms have shaken the doctrine of the storage and direct transformation of starch. The criticisms are directed chiefly against Moscati's analytical methods.

Verzar (2) obtained experimentally a result opposed to Moscati's views. Seeking to prove that the function of the liver is not indispensable for the combustion of carbohydrate in the body, Verzar first tied off the liver, and then injected solutions of either starch or dextrose into the jugular veins of curarized animals. From a study of the respiratory quotient, he concluded that both these substances can be burned under the conditions of the experiment; that is, a preliminary conversion into glycogen by the liver is not a necessity for the combustion of carbohydrate in the body. Again Verzar (4) more definitely attacked Moscati's work. He gave large intravenous injections of soluble starch in rabbits and dogs; 100 cc. 3 per cent solution in rabbits, 250 cc. 3 per cent solution in dogs under 5 kilos. If the starch is injected quickly, either species may show either starch or sugar in the urine. If the starch is injected very slowly (*e.g.*, 1 cc. per minute), neither substance appears in the urine. From respiration experiments, Verzar concludes that the starch is oxidized. The rate and the completeness of oxidation are just the same, whether the starch is injected into the jugular vein or into the portal. He entirely rejects Moscati's results, which were based on iodin tests; and he attributes the mistakes to the uncertainty of such tests. Verzar refers to the results of Wohlgemuth, and bases on them a calculation that the blood-diastase can saccharify even more starch in a unit of time than was injected in his experiments. He concludes that the starch is first inverted, and then burned as sugar.

The above experiments dealt with cooked starch. In the same paper, Verzar found that injections of suspensions of uncooked starch in normal dogs always cause death by embolism. But after partial removal of the pancreas, or even in case of chronic

pancreatitis after trypsin injections, a dog bears raw starch injections safely. The author bases his explanation upon Wohlgemuth's finding of increase of the blood-diastase after partial extirpation of the pancreas.

The discussion of this subject will be continued in the section on diastases.

10. Other Carbohydrates.

For the literature concerning injections of other substances of carbohydrate nature or affinity, reference may be made to Rosenberger. Here it suffices to mention the experiments of Fritz Voit and of Mendel.

Voit injected the hexose sorbinose subcutaneously in a human patient. Out of 10.152 g. injected, 3.735 g. was excreted.

Of pentoses, Voit gave two injections of arabinose, one of xylose, and two of rhamnose. The percentage excreted ranged from 48 to 86 per cent of the injected sugar.

Voit injected the disaccharide trehalose in two experiments, and found an excretion of 15 per cent and 17 per cent respectively of the injected doses.

The trisaccharide raffinose was injected subcutaneously in three experiments. The percentage of excretion was respectively 65 per cent, 66 per cent, and 92 per cent. Voit calls attention to the distinction between this result in the living body and that of Emil Fischer, who found that blood-serum has no action upon raffinose in vitro.

Mendel and Mitchell twice injected a rabbit with inulin intraperitoneally. No reducing substance appeared in the urine. The first injection was 2.8 g., and the excretion amounted to 2.2 g. The next injection was 2.2 g. The inulin recovered amounted to 1.43 g. The authors call attention to the interest of such results, since no inulinase has ever been found in the animal body. It may be remarked in addition, that they could doubtless have obtained larger utilization by means of subcutaneous injections, with the consequent slower absorption.

Mendel and Mitchell made several intraperitoneal injections of isolichenin, and noted a very slow excretion. In one experiment which was followed quantitatively, the injection was $1\frac{1}{2}$ g. isolichenin. The carbohydrate recovered from the urine was equivalent to 0.64 g. dextrin. Excretion seemed to be in the form of dextrin-like compounds.

Mendel and Mitchell made intraperitoneal injections of the glycoproteid ovomucoid. The quantities injected (in a rabbit) were 1.4 g. and 2.6 g. The urines were slightly levorotatory and gave protein reactions. No reducing substance was present.

11. The Paradoxical Law.

In closing the subject of the assimilation-limits of various parenterally injected carbohydrates, it may be remarked that the same paradoxical law applies to the entire group, though in somewhat different degree to the different members. As a rule the injected carbohydrate is utilized to some extent. The existence in the serum or tissues of a demonstrable ferment acting upon a given carbohydrate is not a necessary condition to its utilization. And if with a given dose any utilization of a carbohydrate occurs at all, an increase of the dose causes the utilization of a larger quantity, according to the paradoxical law.

12. Diastases.

A prevalent doctrine is that many cell-functions are performed by enzymes. A favorite method of studying these functions is by means of the enzymes obtained from dead cells. It is like studying the life and habits of a departed race by means of the tools and utensils which they have left behind them. The validity of these methods is supported by certain facts, such as that only the fermentable sugars are true glycogen-formers, and that frequently the intermediate and end-products of enzymic action are the same as those of cellular action. Difficulties are presented by other facts, such as the existence of glycogen in living cells which is quickly broken down by the diastatic ferment of the dead cells, the utilization by the body of sugars for which no ferment is demonstrable, and the practically unchanged diastatic and glycolytic activities of diabetic blood and tissues after death, in contrast to the greatest imaginable disturbances of the economy of sugar and glycogen during life. Various suppositions have been made to explain these discrepancies; the possibility of enzymes which cannot be extracted, and the governing action of the living cell over its various processes. The cell may keep an enzyme separate from its substrate, or control it by an anti-enzyme, or hold it as inactive zymogen till activity is demanded; it may supposedly check reactions at certain points and turn them in some other direction, in a manner impossible to imitate in vitro. The cell in

turn stands under humoral and nervous influences. Differences in the enzymic content or activity of the cells have been called upon to explain the effects of such influences. In particular, such an explanation has repeatedly been attempted for diabetes and for all the principal forms of experimental glycosuria. The glycolytic ferment was mentioned in the previous chapter. When it, as an explanation of diabetes, departed from plausibility, its mantle fell upon the diastatic ferment. The latter is an ideal object of study, first because the substances and reactions concerned — the hydrolysis of starch or glycogen to sugar — are so definite and easily demonstrable, and second because the diastase is considered to exist not only within the cells but also in the blood-plasma. In the latter location it must be independent both of nervous control and of the supposed intracellular control. Its study may conceivably have a bearing not only upon diabetes and glycosuria, but upon the enzymic hypothesis in general.

A strict division of the subject is impossible without breaking into the work of individual authors; but so far as convenient, the literature will be reviewed according to the following classification:

A. Existence and properties of diastases.
B. Origin and distribution of diastases.
C. Alterations of diastase by bodily conditions.
D. Alterations of diastase by carbohydrate injections.
E. Function and fate of diastases.
F. Conclusions.

A. Existence and Properties of Diastases.

This subject goes back to a group of carbohydrate injections not heretofore mentioned. So far as possible, to avoid repetition, researches pertaining chiefly to tolerance and assimilation of carbohydrates were considered in preceding sections, and those which throw light more especially upon the subject of diastases were reserved for this place. The following references to the earlier literature, up to the paper of Böhm and Hoffmann, are taken from Röhmann (3).

Magendie knew of the existence of a starch-splitting enzyme in drawn blood, and sought to demonstrate its existence in the living blood by injections of boiled starch. Within ten minutes after injection, the iodin reaction had disappeared, and an increase of sugar was observed. The quantity of sugar increased up to the fifth hour, then gradually sank, and after 7 hours had returned to normal. The urine remained free from sugar.

Claude Bernard injected 1 g. soluble starch intravenously in a rabbit. The urine showed a heavy reduction test and a strong blue color with iodin. Bernard also injected rabbits intravenously with 30 cc. of strongly opalescent glycogen solution. Glycosuria appeared only once.

Schiff proved that after intravenous injection of dextrin in rabbits, guinea-pigs and frogs, the urine contained sugar, and in some cases also dextrin. After injection of starch paste he found sugar in urine and blood; but no sugar in urine after injection of granulose and glycogen.

Tiegel injected ½ g. glycogen intravenously in rabbits, and never saw glycosuria except in one specially strong animal, in which the glycosuria was marked.

Pavy stated that intravenous glycogen injections increase the sugar of the blood, and after large doses glycosuria occurs.

Tieffenbach considered glycosuria rare after glycogen injections, and caused only by large doses. He invariably failed to find glycogen in the urine.

Böhm and Hoffmann injected cats intravenously with 3 to 10 g. glycogen in 10 per cent solution, as heretofore mentioned; and observed excretion of reducing sugar and achroödextrin in the urine.

Bial is one of the first investigators who studied the question of blood and lymph diastases with improved methods. He reviews more of the earlier literature. Magendie, Bernard, Wittich, Lepine, Seegen, and others considered that the diastase was diffused equally through all the organs. Much of the pioneer work contained errors due to bacterial contamination. Tiegel and Plosz took the ground that the diastase appears in the blood only as a result of destruction of red corpuscles; and against this view the work of Bial was directed. Bial demonstrated that the serum of dogs possesses diastatic power, while the red corpuscles possess none. He also demonstrated a similar diastatic power in the lymph. He studied the properties of the blood-diastase, and found that it breaks down starch, dextrin, and maltose into dextrose; that is, it carries through the whole process, from starch to dextrose, completely. The same amount of dextrose is produced as by splitting with acids.

Schiff is quoted by Röhmann as opposing the belief in the existence of an active diastase in the living body. Schiff had injected glycogen into a rabbit at the moment of death, and ligated the large blood-vessels. But sugar-formation under such conditions is not conclusive; the ferment may arise from mere stasis of the blood, or from injury to cells due to the injected carbohydrate. Schiff accordingly, after injection of glycogen or granulose, bled the animal, receiving one portion of the blood into boiling water, and allowing the other to stand by itself. The boiled specimen showed no particular increase of sugar; the specimen left to itself was rich in sugar. This experiment is somewhat comparable to the persistence of glycogen in living organs, and its rapid disappearance after death. But Röhmann undertook to explain the result on the basis that the blood-diastase had not had sufficient time to act in the first specimen, while in the second the necessary time was allowed.

Röhmann is credited with having proved the existence of diastase in the living body. He despaired of any success with blood, owing to the inevitable abnormalities of some sort consequent upon any experiment. Therefore, at Heidenhain's suggestion, he established thoracic-duct fistulas in dogs, and injected glycogen into a lymph vessel of the leg. There was accordingly no special disturbance of lymph-circulation, and the fluid obtained from the thoracic-duct fistula easily showed that conversion of glycogen into sugar had occurred.

A number of investigators subsequently studied the properties of the blood- and tissue-diastases. The most important work is that of Fischer and Niebel, comprising a series of different animal species, a series of tissues from the different species, and a series of different polysaccharides upon which the effect of the various extracts was tested. Apparently all who have worked with blood or lymph in vitro have deter-

mined the presence of a diastatic enzyme, with the single exception of Abderhalden and Brahm noted below.

B. Origin and Distribution of Diastases.

In this connection, only some of the later work will be reviewed. Other references may be found in the papers mentioned.

Loeper and Ficai studied the subject in 1907. Clerc and Loeper in 1909 ligated the pancreatic duct in 5 rabbits. In consequence, they found first an increase, thereafter sometimes a slight fall of the blood-diastase. The increase is supposed to be due to absorption of pancreatic diastase, but the authors do not consider the pancreas the sole source of blood-diastase.

Ehrmann and Wohlgemuth review the literature concerning the diastase content of the blood of the pancreatico-duodenal vein, including Lepine's claim of a higher content in it than in blood from other regions, and the positive and negative findings of other investigators. Ehrmann and Wohlgemuth found no increased quantity of diastase in the blood of either the pancreatico-duodenal or the portal vein.

Otten and Galloway, working with dogs, found that the blood-diastase sinks rapidly after complete removal of the pancreas, then rises somewhat and maintains a constant level, but never attains the normal height. Their conclusion is that not all of the diastase can be of pancreatic origin; that possibly the diastases play no part in metabolism but are mere waste products.

Gould and Carlson, also working with dogs, reported that ligation of all pancreatic ducts is followed by great increase of the diastatic power of the serum, probably due to absorbed amylopsin. There is next a return toward normal, followed by a secondary rise, and sometimes a third rise. Atrophy of the pancreas is not followed by a corresponding diminution in the diastatic action of the serum. Extirpation of the pancreas generally causes a rapid decrease of blood-diastase, probably due to diminished production. The general harm to all body-cells following pancreas-removal may explain this diminished production. Serous exudates rich in leukocytes, obtained by aleuronat injections, have less diastatic power than the serum. The diastase is not derived from the pancreas nor from leukocytes. The liver is probably an important source.

C. Alterations of Diastase by Bodily Conditions.

Some of the references here necessarily overlap the preceding subject.

Bang, Ljungdahl and Bohm, working with rabbits, reached the conclusion that the diastatic ferment of the liver is probably different from that of the blood and lymph. Quantitatively, the two show non-parallel variations. Less diastase is present in glycogen-rich than in fasting livers, and the authors suggest a teleological explanation from the standpoint of the blood-sugar supply. A rabbit killed by a neck-blow or other nervous concussion has more liver-diastase than one killed by an anæsthetic. The authors find here an explanation for the glycosuria following nerve-injuries. The Bernard puncture causes an increase of diastase within a few minutes; but the quantity quickly sinks, and there must therefore be either a disappearance or an inhibition of the ferment. Stimulation of the central end of the cut vagus causes increase of ferment only at the end of an hour; yet hyperglycemia and glycosuria exist during this hour. The authors think, therefore, that the effects produced through the splanchnics and through the vagus are different; that instead of the

liver-glycogen, the source of the sugar in the case of vagus stimulation is the muscle-glycogen, and the condition is therefore a "muscle-diabetes." The authors studied the effects of poisons upon the liver-diastase. Morphine causes a slight glycosuria with a slight increase of ferment. These effects in the case of strychnin are somewhat greater. Phloridzin does not increase the liver-diastase. Phloretin increases it, but the blood-sugar nevertheless does not rise; therefore the conception of "renal diabetes" in the case of phloridzin is sustained.

Bang (1) studied the behavior of the liver-diastase in diabetes; and, in order to do so, had to change from the rabbits previously used to dogs. The livers of depancreatized dogs, themselves glycogen-free, showed no excessive diastatic action when added to glycogen solutions. The author considers this fact to indicate that diabetes depends not on excessive destruction but on deficient formation of glycogen.

Hinselmann (1) chose to work with diabetic livers which contained approximately the normal glycogen-content, in order to avoid errors due to varying relations of contact between liver-pulp and glycogen-solutions to which it may be added. He therefore removed the liver from dogs about one hour after extirpation of the pancreas, at which time it was found well stocked with glycogen. Contrary to the results of Bang, and to Zegla's findings of diminished diastase-content, Hinselmann found, under the conditions of his experiments, that glycogen-destruction and sugar-formation are much more rapid in the diabetic than in the normal liver.

Zegla concluded that glycogen splitting in the liver is a purely enzymatic process. The enzyme belongs to the liver, and is not derived from blood or lymph. For about 24 hours after death, the quantity of diastase diminishes, and this loss may reach 60 per cent; thereafter, loss does not occur. [Starkenstein (1) succeeded in explaining this loss as a simple adsorption by coagulating organ-protein. By suitable technique, the diastase of the liver remains unchanged by time, like that of saliva and of blood.] Zegla found the liver-diastase increased in phloridzin and phloretin glycosuria, sometimes increased in adrenalin glycosuria, greatly increased after vagus stimulation, less in bled rabbits than in those killed by neck-blow, diminished in pancreas-diabetes of dogs, and probably not diminished in human diabetes.

The paper of Wohlgemuth (5) contains the references to the previous researches in which the author had worked out the method of diastase-determinations which is now in general use.* In this paper, the author finds, by the use of his method, that the blood of a fasting dog has the same diastase-content as that of a fed dog; and the character of the food is without influence upon the blood-diastase. Pancreatic activity induced by acid or secretin is likewise without influence. Tying of all pancreatic ducts causes a marked increase in the blood-diastase, even when the animals afterward fast for a long period. Tying one duct causes a less and briefer rise. Partial pancreas-extirpation may produce a rise. Total extirpation of the pancreas results in a very marked fall of the blood-diastase in many cases, but not invariably. Adrenalin, phloridzin or phloretin, and asphyxia are without effect upon the blood-diastase. Wohlgemuth believes that the blood-diastase is derived not only from the pancreas, but also from other organs, such as the intestine, salivary glands, liver, muscles, and kidneys.

Wohlgemuth and Benzur, using rabbits, found no increase of diastase in the blood as a result of phloridzin. There was normal as often as increased content in the liver, but a marked increase in the kidney. They therefore conclude that an increased

* Reference may also be made to Hawk (3), concerning a modification of this method for the feces.

ferment activity in the poisoned kidney accounts for the glycosuria. [Before such evidence can be accepted, it will be necessary to know whether the kidney derives the sugar in phloridzin glycosuria from glycogen; or if from some other substance, whether the diastase has any action upon this unknown substance.]

Wynhausen (1) reviews the diastase literature rather extensively, and reports examination of the blood-diastase in 88 human patients. Of these, 31 had diabetes; the other 57 had various other conditions. The amount of diastase as expressed in diastatic "units" was very variable. There were no fixed differences between diabetics and non-diabetics, nor between light and severe diabetes.

Schirokauer (1) used various means to produce fever in rabbits, and found the diastase content of the blood and liver in all cases normal. He concludes, from this evidence, that the glycogen diminution characteristic of fever is due not to increased destruction but to deficient formation.

Macleod and Pearce, in a series of papers covering an extensive series of researches, reported numerous facts concerning the distribution of glycogenolytic enzyme in various body-fluids and tissue under a variety of experimental conditions. A few of their results are as follows. The nutritive condition of the dog has no influence on the glycogenolytic power of the serum or of the liver-extract. Plasma and serum possess the same amount of diastase. Serum from the carotid artery and from the pancreatico-duodenal vein possess equal amounts. Stimulation of the splanchnic nerve (in the dog), while causing marked increase of sugar in the hepatic-vein blood, does not cause any increase in the glycogenolytic power of extracts of liver prepared in various ways. The blood from the liver possesses also the same glycogenolytic power before and during stimulation of the nerve. The authors take position against Bang and his pupils. They conclude that modifications in the glycogenolytic activity of the liver do not depend on changes in the amount of diastase, but "on changes in the conditions under which a constant amount of this ferment is acting."

Starkenstein (1 and 2) quotes from Wohlgemuth, that there is only one diastase in the whole body; no distinction is demonstrable between the enzyme of saliva, liver, blood, pancreas, and intestine. Starkenstein concurs with Macleod and opposes Bang. He has found no appreciable difference in the diastase after piqûre, adrenalin, hemorrhage, and the various other conditions studied. Livers of normal rabbits are somewhat variable in their diastase content. Livers of bled animals contained more diastase than those of animals killed by neck-blow. Experimental glycosurias are not due to an increase of diastase. His own attempts and those of all others by experiments in vitro to find an explanation of adrenalin glycosuria have failed. A modifying action of lipoids is not demonstrable.

Milne and Peters (2) found a marked diastatic power in normal dog-serum, which converted glycogen into glucose. This power was not altered after a large meal, or after administration of large quantities of dextrose, or in fasting, or in phloridzin glycosuria. Contrary to other authors, they found it slightly or even markedly increased after total pancreatectomy.

D. Alterations of Diastase by Carbohydrate Injections.

For completeness, there will be considered here the changes reported not only in the diastatic powers but also in other activities of the serum, in consequence of carbohydrate injections.

In chronological order, the first discovery is that of Weinland, concerning the inverting power which is acquired by the serum of dogs after repeated injections of

saccharose, and which normal dog-serum does not possess. This work was discussed in the section on saccharose. Later investigators have substantiated the claims of Weinland concerning the production of invertin, but have overthrown his claims of an increased utilization of saccharose, as a consequence of repeated saccharose injections.

Wassermann and Citron used glycogen injections in rabbits to investigate the possible existence of amboceptors for carbohydrates. The animals were given three or four injections a few days apart, with increasing doses. The highest dose subcutaneously was 0.4 g. Smaller doses were employed in intravenous experiments. They concluded that glycogen with normal serum has a slight complement-fixing power, in the true sense of the term. They could make out no distinction between glycogen of the animal's own species and that from different species. The question whether their injections as described resulted in an increase of the supposed amboceptor in the blood is answered by the authors, a little doubtfully, in the affirmative. The increase observed was small.

It may be remarked that if the increase of amboceptor was small, the injections also were small. In their experiments the authors assumed not only that glycogen might act as an antigen, but also that it will be as powerful an antigen as toxins and protein substances. The latter assumption may be untrue.

Mendel and Mitchell, after subcutaneous injections of saccharose repeated at intervals for as long as 7½ weeks, found no increase of utilization of saccharose by either dogs or cats. They confirmed Weinland to the extent of finding that after repeated saccharose injections the serum may acquire a slight inverting action; but the majority of their results were negative.

Abderhalden and Brahm take a distinctive and isolated position, in claiming to have proved in numerous experiments that normal serum of a grown dog does not decompose starch (nor saccharose, raffinose, lactose). Details concerning the mode of preparing the serum are not stated. But they find that if saccharose is given to a dog parenterally, the serum acquires the power of inverting saccharose in vitro. Herein they confirm Weinland. The effect was not increased by a few repeated small injections extending over a number of days. A similar effect results from the injection of starch; and the serum from starch injections not only splits starch but also inverts cane sugar, in vitro. Their results were inconstant, sometimes positive, sometimes negative.

Abderhalden and Kapfberger studied the subject more exhaustively. They review former papers in their series, showing that repeated subcutaneous injections of fat are without effect upon the serum; that albumin or peptone injections give rise to a non-specific power of the blood to break down any albumin or peptone; that injection of saccharose, lactose, or starch produces a similar non-specific, diastatic and inverting power of the serum for carbohydrates; and that the serum in consequence of protein injections acquires no power of digestion of fat or carbohydrate. The best effects of saccharose are obtained from small doses. When they used only 10 cc. of a 5 per cent or 10 per cent solution subcutaneously, or 2 cc. intravenously, the results were always positive. Raffinose injections gave negative results. Injection of either saccharose or lactose seemed to enable the blood to split both, though the precise effects on lactose were not determined. After subcutaneous injection, the blood acquires inverting properties in 7 or 8 hours; after intravenous injection, as early as 15 minutes. This power continues for about 14 days. After a first injection, the urine was dextrogyrate for 11 or 12 hours, then became levogyrate. After

3 or 4 injections, the levorotatory change occurred in 9 hours. On dialysis, the inverting ferment was found in the dialysate. After keeping 3 days at 4° C. the splitting power was somewhat diminished. By heating 15 minutes at 60° degrees it was inactivated. Serum and plasma are equally efficient. Blood standing 16 hours with saccharose develops no splitting power. The origin of the ferment in the body is therefore not in the blood or its formed elements. The injections give rise to ferments which previously were either absent or unable to act.

E. Function and Fate of Diastases.

Many of the authors who express opinions concerning the function and fate of the diastases touch also upon the first three topics discussed.

Fichtenmayer considered that most of the subcutaneously injected glycogen was broken down by local ferment action. Mendel attributes importance to tissue enzymes.

Cavazzani and Finzi found that after vagus stimulation, dextrose in the blood of the hepatic veins is increased, but the amylolytic ferment is unchanged. If the ferment is increased in the liver as a result of the stimulation, it at least does not enter the blood. Whether it is formed and retained in the cells is considered doubtful. The authors think it possible that the cell contains inhibitory substances to control the ferments, otherwise their action might last longer than necessary.

Schlesinger (3) concludes that the greater part of the diastase of the blood comes from the pancreas. But no simple relation between this ferment on the one hand and increased glycogen-destruction or glycosuria on the other hand, can be demonstrated.

Carlson and Luckhardt find a descending scale of diastase content in the body-fluids as follows: serum, thoracic lymph, neck lymph = lymph from limb, pericardial fluid, cerebrospinal fluid. There is no constant difference between the diastase-concentration of the portal and of the hepatic blood. Stimulation of the central ends of the vagi may cause a slight increase. Extirpation of the pancreas does not affect the concentration of the blood or lymph diastases. Anæsthesia causes a slight decrease. There is no relation to food, and no relation to the rate of oxidation. On this basis, the authors conclude that the diastases are waste-products, on their way to destruction or elimination.

Schirokauer and Wilenko mention the two opposing views of cell-function, viz. that of a specific vital activity as supported by Noël-Paton and Cavazzani, and that of purely fermentative processes, as upheld by Bernard, Wittich, and Pavy. They consider that the work of Dastre and of Pick has decided that glycogen destruction occurs in the cell and not in the blood, but by means of a ferment, which may be called the true liver-diastase.

Moeckel and Rost have contributed one of the most complete investigations in all the literature of the diastases. Some of their findings in brief are as follows. In different species, the concentration of diastase corresponds to the digestive power. Hemorrhage produces no change. The placenta is impermeable to diastase. It is increased by cold, also by hunger. Administration of diastase by mouth or subcutaneously has no effect on the blood-diastase; but administration intravenously or intraperitoneally increases it. Pancreas extirpation diminishes the diastase. Pilocarpin increases it. Phloridzin has no effect except when combined with starvation; in this event, fatty liver and diminution of diastase are coincident. Strych-

nin generally increases diastase. Adrenalin is without effect. Piqûre and other nervous influences are without effect. The diastase is generally diminished in human diabetes. In case of renal impermeability there may be a moderate increase of blood-diastase. The authors are of opinion that the blood-diastase is a product of the metabolism of the cells, which comes from the leukocytes, pancreas, liver, and probably a number of other organs; that it is partly disposed of in the system and partly excreted in the urine; and that it has no special significance and serves no function in the organism.

Wynhausen (2) reported a series of examinations of the urine for diastase, especially in diabetes and in nephritis. He ascribes to the method a little prognostic value in diabetes, unless complicated by nephritis. The quantity of diastase excreted is supposed to be diminished in both diabetes and nephritis.

A. Rosenthal concludes that normal urine has a diastatic power; that the diastase may decrease with decreased permeability of the kidney, and increase with increased permeability; that the diastase is generally diminished in diabetes, but not always.

Finally, the opinions of authorities on diabetes and on metabolism are of interest.

Von Noorden [(3), p. 533] says in discussing the effects of piqûre: "It has been suggested that the nerve stimulus may cause an increased formation of diastatic ferment." And on page 536: "We regard it as now proven that it is a diastatic ferment in the liver-cells which thus converts the glycogen."

Pflüger (1), on page 375, mentions the discovery of the liver-diastase by Wittich, and the practical certainty that the sugar-formation in the liver postmortem is an enzymic, not a "vital" process. The following pages describe Pavy's defense of this thesis against Foster and Noël-Paton. On pages 393–94, Pflüger states his belief in a regulation of the ferment-activities of the liver-cells by the nerves. A splitting of molecules under nervous influence gives rise to the ferment, which is a decomposition product of the protoplasm.

The views of Lepine [(1), pp. 78, 136, 188] resemble those of most other authors.

F. Discussion and Conclusions.

These may be grouped as follows:

I. Concerning blood-diastase.
II. Concerning the rôle of the kidney.
III. Concerning tissue diastase.

I. Concerning Blood-Diastase.

Except Abderhalden and co-workers, all authors have found a diastase in shed blood. Its existence in normal circulating blood is generally assumed but not proved. The evidence is open to criticism as follows.

(*a*) Injections like those of Bernard and Magendie prove nothing. Hyperglycemia results from injection of various substances; it is not necessarily due to splitting of the injected starch or glycogen. In view of the small quantities injected, the follow-

ing seems certain; a *sudden* saccharification of the starch or glycogen could not cause hyperglycemia lasting for 7 hours as stated; a saccharification *continuing* for 7 hours could not keep up the degree of hyperglycemia represented. The iodin reaction might disappear by reason of deposition of the starch in organs or its change otherwise. Above all, these methods do not rule out two possibilities, (1) that the injected starch may be split by living cells rather than by an enzyme; (2) that an enzyme if present may be an abnormal product resulting from injury caused by the injection.

(*b*) Röhmann's injections into lymphatics are not perceptibly more conclusive than injections into blood-vessels. A diastase if present might conceivably arise from the injured lymphoid or endothelial cells, or even from chemical changes in the lymph itself. Especially, the injected substance necessarily passed through a series of lymph-glands, and it is the recognized function of these glands to act upon substances, especially foreign substances, contained in the lymph.

(*c*) Moscati's work if confirmed would militate against the existence of a circulating diastase. It is worthy of repetition by means of better methods for recognizing starch in the presence of glycogen, both for the present purpose, and for the question whether the pathological deposits in diabetes are due to circulating glycogen.

(*d*) Verzar's study of the respiratory quotient does not necessarily prove that the starch itself was burned. Even saline injections, as Verzar showed, affect the gaseous exchange. Above all, there is no evidence whether the starch was split by living cells or by an enzyme, or whether the enzyme if present is a normal constituent or the result of injury.

(*e*) Moeckel and Rost's finding of increased blood-diastase after intravenous or intraperitoneal injections of diastase may represent a circulation of the foreign diastase for a certain time, but quite possibly is the result of injury. It is not improbable that an increase of the blood-diastase might be demonstrable after similar injections of a proteolytic or lipolytic ferment.

Attention seems never to have been called to the important bearing of subcutaneous (or intraperitoneal) carbohydrate injections upon this question; and it was in this connection that the subject was introduced. Wohlgemuth's method of diastase determination is universally accepted. Verzar, using this method,

calculated the diastatic activity of the blood of his dogs. He injected intravenously a 3 per cent starch solution, at the rate of 1 cc. per minute, to the amount of 250 cc. in dogs under 5 kilos. He calculated that the diastase of the dog's blood can saccharify even more than this quantity of starch per minute. He deduced from this calculation and the respiratory quotient that the injected starch was completely split by the blood-diastase and burned by the body as sugar. These findings should be compared with experiments, for example, such as Mendel and Mitchell's experiment 19. Here a bitch weighing 8½ kilos received an intraperitoneal injection of 6.4 g. soluble starch. The dog was considerably larger than Verzar's and the amount of starch was smaller. Mendel and Mitchell report an excretion of dextrin for fifteen hours in this case. It is to be remarked that the excretion is still slower when the injections are subcutaneous. The most striking records are those of Fritz Voit. The subcutaneous injection of 11.57 g. soluble starch in a human patient caused a dextrin excretion continuing for 46½ hours. In another instance an injection of only 5.78 g. soluble starch was followed by excretion of dextrin for 33 hours. Mention may also be made of his injection of 14.57 g. erythrodextrin, followed by excretion for 19½ hours; and his two injections of about 10 g. achroödextrin, followed by excretion for 13½ and 16 hours respectively. The excreted substance in every case was achroödextrin.

Starch and the other polysaccharides are slowly absorbable substances. When injected subcutaneously or intraperitoneally, they reach the blood very slowly and gradually. At the site of injection, they may be acted upon by living cells, and at the same time the injury produced by the injection may give rise to abnormal ferments. Authors have, in fact, analyzed the fluid at the site of injection and demonstrated a local splitting of the injected substance. Fichtenmayer with his huge injections gained the impression that a large proportion of the total quantity is broken down locally. Certainly not all the injected dose reaches the blood-stream. That which reaches it, does so with such slowness that pathological changes are not produced in the blood. Contrary to Verzar's calculation, these small traces reaching the blood are not split by the supposed diastase, but reach the kidney in quantity sufficient to be excreted. By comparing Verzar's calculation with the experiments of Mendel and of Voit, it is evident that either the calculation of the quantity of diastase is wrong, or

else the diastase found in the shed blood is not present in the circulating blood. In point of fact, the discrepancy is too great to be explained as a simple error of calculation. In Voit's case, for example, supposing that no starch was destroyed locally, if a reckoning be made of the 11.57 g. of injection and the 46½ hours of excretion, it is seen how infinitesimal is the quantity of starch reaching the blood, in comparison with the diastatic power supposed to be possessed by the blood. It would appear that the circulating blood either contains no diastase, or that the diastatic power is less than estimated from calculations in vitro. Authors have generally assumed that the diastatic and glycolytic ferments are more efficient in the body than outside; to attempt the opposite assumption will weaken the case. It may be suggested that the enzyme in the living blood is neutralized by an anti-enzyme or something of the sort; but the whole is equivalent to the conclusion that an active diastase does not exist in the circulating blood. As further evidence in this direction may be recalled the fact that the diastatic power of diabetic blood in vitro is little if any changed, yet traces of glycogen may exist free in the plasma.

Schiff looked upon the diastase as the first sign of death of the blood, on a par with the coagulating ferments. The results of parenteral injections of polysaccharides would tend to confirm his view that an active diastase does not exist in the normal blood.

II. Concerning the Rôle of the Kidney.

It seems possible that the kidney may play a significant part in the phenomena which follow the parenteral injection of foreign carbohydrates. In this topic is included also a point omitted under the preceding one. That is, the argument may be made that the blood contains an active diastase, but that the time between the absorption of the carbohydrate and its arrival at the kidney is too brief for the diastase to complete its work. While this possibility may not be excluded, account must be taken of the infinitesimal quantity of carbohydrate absorbed per unit of time, and its absorption into the venous blood, where it must pass to the heart and be mixed with the main mass of the blood, then pass through the lungs, and then only a portion of it be carried directly to the kidney, while the greater portion makes the round of the systemic circulation.

The stimulus of a foreign substance excites the kidney to activity. The function of the kidney with respect to such substances is primarily elimination. But a further part of the renal work may be assumed to be the breaking down of large molecules into smaller for the sake of easier disposal, and furthermore the reclaiming for the organism of as many of the valuable decomposition-products as possible. This function of the kidney may be overtaxed, as when large intravenous injections of starch or glycogen cause these substances to appear unchanged in the urine. But a function of this sort seems indicated as a possibility for saccharose in the dog and for polysaccharides in other species.

According to this assumption, a slight power of splitting saccharose may be attributed to the kidney of the dog, but not to the kidney of other species. When a dog receives a subcutaneous saccharose injection of less than 1 g. per kilo, generally only saccharose appears in the urine. Presumably the invert sugar formed by the kidney is here saved by the kidney, either by not letting it reach the urine at all, or by resorption in the convoluted tubules. If a large injection of saccharose is given subcutaneously in a dog, reducing sugar always appears in the urine. Presumably the kidney here has produced from the large dose more invert sugar than it can retain or resorb; also the sugar in the urine is chiefly levulose, on account of better retention or resorption of dextrose. The same large dose given intravenously causes less reducing-power in the urine than when given subcutaneously, presumably because the intense stimulation of the high percentage of saccharose in the blood, with the copious diuresis which it occasions, hurries the kidney so that it has no time to split many molecules; all it can do is to dump them overboard bodily as fast as possible. When saccharose injected subcutaneously or otherwise causes elimination of reducing sugar, three stages may be distinguished: first, excretion of saccharose only; second, excretion of saccharose and reducing sugar; third, excretion of saccharose only. The second stage is the period of principal excretion; it is the time during which the kidney is forming more invert sugar than it can retain or resorb. The first and third stages are those of initial rise and final fall of the sugar-elimination; the amount of saccharose is less, and the kidney is able to retain or resorb the invert sugar formed from it.

In support of this view, attention may be directed to an experiment of Mendel and Kleiner. In their experiment 34, the intra-

peritoneal injection of 22.67 g. invert sugar (representing 1 g. saccharose per kilo) gave rise to no reducing power in the urine; whereas previous intraperitoneal and subcutaneous injections of the same dosage of saccharose in the same dog had repeatedly and uniformly caused the excretion of reducing sugar. According to well-known laws, the invert sugar must reach the blood-stream more rapidly than the saccharose. If this one experiment can stand, any other than a renal origin for the reducing sugar in the urine of dogs after saccharose injections seems to be ruled out. I have spoken of the case for saccharose as probable rather than certain, only because this dog's tolerance for levulose in the form of invert sugar seems to me unusually high. Nevertheless, the fact reported in this animal requires explanation, and any other than a renal origin for the reducing sugar seems impossible. Further experiments of this type may throw further light on the question.

Concerning the polysaccharides, reference may again be made to the record of my Dog 34 for April 7. The injection of dextrin here was about 8 g. per kilo, or not far from the assimilation-limit of dextrose in the dog. The record may conveniently be summarized as follows.

Dog 34.

April 7, injection 9:30–10 a.m. Evening urine 220 cc. Reducing sugar 0.56 per cent (as dextrose). Achroödextrin present.

April 8, morning urine 150 cc., reducing sugar 1.3 per cent (as dextrose), achroödextrin present. Evening urine 260 cc., reduction test slight, slight achroödextrin.

It is quite possible that an injection of this quantity of dextrose might cause an excretion of 0.56 per cent in the evening urine. But such an injection of dextrose, between 9:30 and 10 a.m. of one day, would never cause a reduction of 1.3 per cent in the morning urine of the following day, nor a slight reduction test in the urine of the following evening. If the dextrose were disturbed in fractional doses through 24 hours or longer, to imitate the slow absorption of the dextrin, there would be no glycosuria at all. Over and above this is the loss of part of the dose of erythrodextrin in the form of achroödextrin. It is obvious that injected dextrin gives rise to greater mellituria, and for a longer time, than injected dextrose. The question arises whether the reducing substance

is dextrose, or whether it may be some more difficultly assimilable sugar, perhaps maltose. It is quite probable that maltose will be found in the urine. But in view of the known facts concerning the assimilation of various sugars on either subcutaneous or intravenous introduction, it seems to me improbable that a mellituria of this degree and duration can be explained by a sugar-formation either at the site of injection or in the blood-stream. Rather, a splitting action on the part of the kidney seems the best explanation. The renal cells break up the large molecule for excretion, and also save as much sugar as they can. This view is further supported by the results of intravenous injection of glycogen or erythrodextrin; for here only massive doses cause the injected polysaccharide to appear in the urine; instead, achroödextrin is excreted, with or without sugar. None of the evidence is yet conclusive. The kidney alone cannot explain the quick disappearance of the iodin reaction from the blood after intravenous injections; the action of other organs or a ferment must be considered. Other explanations may be possible for other phenomena. But the splitting action of the kidney seems at least an attractive possibility.

The hypothesis of the renal origin of the mellituria caused by polysaccharides offers a point of special interest in its possible analogy with phloridzin. Heretofore, phloridzin glycosuria has stood practically as a condition sui generis. Its radical difference from the other forms of glycosuria classified as "renal" is obvious. There is evidence to indicate that the condition consists in the presence of an abnormal compound or complex, from which the kidney splits off glucose. This view may be somewhat strengthened, if it can be shown that the kidney splits off and excretes sugar from other large foreign molecules, viz., the polysaccharides. It must be recognized that the mellituria resulting from dextrin or glycogen is much less than from phloridzin, but such a difference may be readily explainable by differences in the ease with which the sugar is separated from its combination. In the case of the polysaccharides, a deep cleavage of the molecule through several stages is required; in the case of phloridzin, the hypothetical combination must be one from which sugar is quickly and easily split off. The resemblance is not proved, but it seems an attractive possibility. Some of the lines of experiment by which it can be tested are self-evident. Conversely, it might prove of interest to repeat Röhmann's experiment, using phloridzin

instead of glycogen. It was previously suggested that the lymph-glands might, like the kidney, break down the polysaccharide molecule. There is perhaps a bare possibility that they might behave like the kidney also toward phloridzin.

III. Concerning Tissue Diastase.

The evidence has suggested that the blood-diastase may have no normal existence, but may be entirely a product of death or injury. The existence of a diastase in the normal living tissues has less support than its existence in blood; formal proofs, such as attempted by Röhmann and others for the blood, are impossible for the tissues. According to authors quoted, the blood-diastase and the tissue-diastase are identical. If it shall be proved that the blood-diastase is solely a pathological or postmortem product, the suspicion is thereby raised that the tissue-diastase may be nothing more. The possibility is important for diabetes, because so many experiments concerning diabetic problems have been performed with dead organs or organ-extracts, or under conditions fully as abnormal as those which cause the diastatic ferment to appear in the blood. Also, a question of this sort regarding the diastase extends by inference to other enzymes. None of the methods mentioned do or can disprove the possible existence and function of enzymes in living cells. But they may well serve to emphasize the difference between living and dead cells, and the difficulty of drawing conclusions concerning the former from the latter.

One fact is established firmly by the numerous researches reviewed. That is, that the enzyme-content of dead cells bears no relation to the functional state of the living cells. The study of the diastases has given no explanation of diabetes or of any form of experimental glycosuria.

CHAPTER III.

REPEATED INJECTIONS.

THIS chapter will deal with the effects of long-continued excess of sugar in the circulation of normal animals. It is part of an attempt — repeated through several chapters — to give an experimental answer to various questions pertaining to such an excess of sugar. There is a widespread belief, or at least suspicion, concerning the toxicity of sugar, the possibility of injury to the organs or functions of the body from the physical or chemical properties of the sugar. Such a belief has some intrinsic plausibility, and is supported by a certain amount of clinical and experimental evidence. The views expressed pertain to alimentary intoxication (Finkelstein), obesity (von Noorden), anatomical changes in the adrenals or pancreas (Marrassini and others), and especially to diabetes and its complications (numerous authors). At this place it is desired to review some of the clinical and experimental opinions and observations concerning the relation of hyperglycemia to diabetes, its symptoms and complicatons.

1. Influence of Excess of Sugar in Producing Diabetic Complications and Symptoms.

In general, the preponderance of opinion on this subject is strongly in favor of the toxic action and etiologic importance of the excess of circulating sugar. The individual views will be considered in succession, first on the general subject, and then as respects each of the commonest complications taken separately.

A. CONCERNING COMPLICATIONS IN GENERAL.

Naunyn is an authority who has assigned considerable importance to hyperglycemia in the causation of the complications of diabetes. Von Noorden [(1), p. 175] refers to Naunyn as a typical exponent of this view, and as attributing to hyperglycemia the following effects: neuralgias and similar pains, angina cordis, asthma, itching, eczema, impotence, gangrenous inflam-

mations, scurvy, furuncles, carbuncles, cataract, retinitis, and abnormal sensations of hunger and thirst. Von Noorden himself takes a rather neutral position, though always admitting and sometimes affirming the etiological rôle of sugar. He mentions (l. c.) three possible causes for the complications of diabetes, viz., the impaired nutrition, the excess of sugar, and the presence of unknown toxins. He decides that there may perhaps be various causes; sugar is at any rate not the sole cause; and it is of practical importance in treating the complications not to be content with a mere reduction of the hyperglycemia, but to use other measures as well. So also in considering the individual complications, he has generally stated conservatively that "some say" sugar is a cause.

Pflüger took a positive and even extreme position in favor of the toxicity of sugar, and its etiological importance with respect to many symptoms and all complications of diabetes. A remark on page 456 of "Das Glykogen" conveys his general attitude: "It cannot be denied that the sugar-content of the body-fluids gradually damages all functions of the organism. Wounds heal badly or not at all; muscular strength diminishes; the sexual power fails."

Minkowski, apparently, has never taken a positive stand on this question. He does not subscribe to Pflüger's belief that it is the excessive sugar-content of the tissues which prevents wound-healing after extirpation of the pancreas.

Pavy (1) (also in other published writings) has taken an extreme affirmative attitude. For example, page 101: "There is indisputable evidence to show that sugar acts as a toxic agent if allowed to traverse the system. Ill-effects of various kinds follow its presence in uncontrolled cases of diabetes, which disappear when the system is brought, by dietetic means, to a natural state as attested by the urine becoming free from sugar." Again, page 103: "It does not seem to be realized in the manner it ought to be that the sugar traversing the system is behaving in the pernicious way it does. An abnormal state such as that resulting from the filtration of sugar through the system from the food to the urine — for this is the condition that is virtually existing — cannot do otherwise than inflict harm." "Simply by bringing down the sugar, which is at the root of the various troubles belonging to the disease, their subsidence ensues, and brings about a speedy conversion of a sorely stricken state into one

of ease and cheerfulness." Again, page 108: "The sugar traversing the system constitutes, certainly in the alimentary form of diabetes, the cardinal deleterious factor of the disease." "Virtually it is the toxic action of the sugar present in the blood that gives rise to the ill effects upon the system produced by diabetes. Various kinds of structural damage are known to be inflicted, and they stand in keeping with those produced by alcohol and other toxic agents. Indeed, as regards the kidney and the nerves, the closest analogy is to be traced between the effects of alcohol and of sugar. In diabetes, sugar is holding a wrong position in the body, and in this wrong position it constitutes a true toxic agent — a fact that is not generally realized in the manner it should be." Again, page 114: "As previously stated, we only know of diabetes through the effects produced by the sugar present in the system. Necessarily there must be a primary condition to lead to the abnormal presence of the sugar, but this does not in any way reveal itself except through the effects of the sugar." "To the sugar, undoubtedly, must be attributed the various troubles met with in connection with diabetes." And again, page 115: "When the production of these acids sets in, we have a second toxic agency to deal with; but previously, as I have said, all the tangible conditions appertaining to diabetes arise from the sugar abnormally present in the blood. The sugar constitutes as much a direct toxic agent in the system as alcohol, lead, arsenic, mercury, etc. A great variety of morbid effects, wrought upon different parts of the system, are produced by it, in like manner as occurs with alcohol, and in all instances the only means of effecting their removal is by working through their prime cause and by getting rid of it from the system."

In this connection, it may be mentioned that Scott, who worked with subcutaneous injections of dextrose, places dextrose with phosphorus in the category of "protoplasmic" poisons.

Kleen (p. 71) says: "Persons suffering from true diabetes, who cannot be persuaded to adhere strictly to a proper diet and who constantly present glycosuria (and hyperglycemia) *may* live in fairly good health for more than twenty years. This single fact *proves* that hyperglycemia per se cannot be a very powerful nocens. Its worst effect is probably the retaining firmer than is the normal the water in the blood-vessels, and thus, to a certain extent, desiccating the tissues. This causes some disturbance in the nutritive state and the functional power of the organs; it

may, *e.g.*, bring about cataract and contribute to the development of gangrene, suppuration, and other disintegrating processes, or of neuritis and other 'parenchymatous' changes. The hyperglycemia may also be, in fact, responsible for the diabetic endarteritis and the arteriosclerosis. The hyperglycemia, however, which in most cases is quite moderate, generally takes a very long time to bring about these changes." Also on page 81, Kleen assigns to the hyperglycemia a share in lowering the general resistance of the diabetic patient.

Weiland (2) holds hyperglycemia an etiological factor in complications of diabetes, such as furunculosis, neuritis, etc.

Falta [(5), p. 162] says: "We are accustomed to refer many, indeed most, of the secondary phenomena in diabetes to hyperglycemia: the lancinating pains, furunculosis, pruritus, the falling out of the teeth, the failure of hearing, the premature cataract, the impotence, the vulnerability of the tissues, and the early arteriosclerosis with gangrene. But the significance of hyperglycemia is far greater than this, in that long-continued hyperglycemia increases the disturbance of metabolism, thereby establishing a vicious circle. We understand, accordingly, why all these results of hyperglycemia, and one especially, namely gangrene, are to be found even in apparently very mild cases of diabetes. These individuals may excrete a few grams of sugar daily, but they may have had diabetes and accordingly hyperglycemia for fifteen years; thus we perceive the desirability, even in cases of the diabetes of old age, of not being content when the excretion of sugar has been reduced to a few grams, but of insisting on complete disappearance of sugar."

Herter wrote (p. 389): "In spite of the paucity of our knowledge of the pathological effects of a hyperglycemia, I think we are justified in believing that the presence of a large excess of sugar cannot be a matter of indifference to the organism."

B. Concerning Particular Complications.

I. *Impotence* (according to Naunyn, p. 233) may exist in young diabetic men long before the exhaustion of general strength occurs, and sexual power may return after treatment has produced diminution or disappearance of the glycosuria. Tommasi and also Bussard are here quoted as supposing that the cause of the impotence is the killing of spermatozoa by the excess of sugar, but their opinions are refuted by Naunyn himself.

Parisot has made the most recent clinical study, in both male and female patients. Impotence and sterility may occur very early in the disease, and stand in no regular relation with either glycosuria or cachexia.

II. *Arteriosclerosis.* — As noted above, Kleen, Falta, and others suggest hyperglycemia as a causative factor in diabetic arteriosclerosis.

III. *Lowered Resistance to Infection and Delayed Healing of Wounds.* — Pflüger [(6), p. 186], in regard to depancreatized dogs, speaks of "die durch den Zuckergehalt der Säfte verhinderte Heilung der eiternden Wunden." Such expressions are common with Pflüger; but he adduced no evidence to show that the sepsis and the failure of wound-healing in diabetic dogs are due to the hyperglycemia rather than to other known or unknown causes.

The lowered resistance of diabetic tissues is not so greatly feared by surgeons now as formerly, since it has been shown that with the present efficiency of aseptic technique, extensive operations may be performed on diabetics with no excessive danger of infection and with perfect healing of the wounds. Karewski is one of a number who have written articles dealing from the surgeon's standpoint with operations on diabetics, their indications and contraindications, favorable and unfavorable conditions, and other features. He mentions, as do many of the texts on diabetes, that post-operative coma is generally more to be feared than infection. As to sugar, Karewski mentions that bacteria grow best in media containing sugar, therefore the higher the degree of glycosuria the greater the danger. Nevertheless, the greatest danger is in the poor general condition; a patient in good general condition with high glycosuria may do better than one with cachexia and low glycosuria. The sugar alone is not a safe guide. Too strict antidiabetic diet may increase the danger of coma. A patient who has been made sugar-free and who appears strong and well may after operation go directly into fatal coma.

More recently, Umber has written concerning the indications and prophylaxis for surgical operations upon diabetics, and has concluded that not even severe diabetes with acidosis is a positive contraindication. The subject is of importance in connection with Chapter XXII.

Sweet found a marked diminution of the hemolytic and bactericidal properties of dogs' blood after removal of the pancreas. Complete extirpation of the organ is just as essential for the

occurrence of this change as it is for the occurrence of diabetes. The diminution in the properties mentioned was not obtained in normal animals made glycosuric by adrenalin or phloridzin. For the sake of comparison, reference may be made to the work of Mlle. Fassin, who reported diminution of alexin after removal of the thyroid, and increase on thyroid feeding.

Da Costa and Beardsley, examining the blood in 74 cases of human diabetes, found the average, on the basis of the opsonic index, only about one-third the normal. It was lowest in the severest cases, those with the highest hyperglycemia, or with coma.

The most recent article on the causes of the diminished resistance of diabetics to infection is by Handmann. His experiments were all *in vitro*, and he concludes: (1) Blood to which has been added ½ to 1 per cent dextrose is no better culture-medium for staphylococcus than normal blood. (2) Adding dextrose to blood does not diminish the bactericidal powers of the blood, provided the percentage of sugar is no greater than may occur in the body of the diabetic. (3) By similar addition of dextrose, no effect upon the opsonins can be demonstrated. (4) The diminished resistance of many diabetics to infections probably depends not entirely nor chiefly upon injury to the antibodies of the blood or of the body-fluids, but upon local tissue-injuries. In the final analysis, therefore, it is not a humoral but a cellular problem.

Handmann's evidence is as conclusive as can be expected of experiments *in vitro*, which can, however, never decide the question. All his conclusions are well-supported, including the fourth, to the effect that he has proved the problem to be cellular and not humoral. But how the cellular injury arises, whether it is the consequence of hyperglycemia or of other causes, is a different problem, which Handmann did not touch.

The converse of such experiments with body-fluids, namely the effect of sugar upon pyogenic bacteria *in vitro*, has also been tested by a number of investigators. Theobald Smith found that sugar is harmful to certain organisms, including pus-cocci; 1 per cent dextrose in the culture medium may cause them to die out, by reason of acid formation. Kayser, also Grossman [both of these quoted by Lepine (1), p. 600] find the staphylococcus attenuated in virulence by cultivation on media containing sugar. But media containing, as in these instances, from 2 to 5 per cent sugar, do not represent the conditions in diabetic tissues.

Experiments *in vivo* are more important than those *in vitro*, if carried out under suitable conditions.

Leo (1) undertook to draw conclusions from experiments with phloridzin, in which the "diabetic" animals (rats and mice) showed less resistance to anthrax and other infections than did the normal controls. But, as critics have pointed out, phloridzin poisoning does not cause hyperglycemia, and the experiments therefore have no value as respects the influence of sugar in infections.

Grawitz found that certain fungi develop much more readily after intraperitoneal injection in rabbits, if the animals have first been made "diabetic" by injections of amyl nitrite. But among the various harmful effects of amyl nitrite poisoning, there is no reason for singling out the slight hyperglycemia and ascribing the lowered resistance to it.

Bujwid demonstrated that Staphylococcus aureus grows less luxuriantly in 5 per cent dextrose-media than in absence of dextrose; and concluded therefore that the sugar in diabetic tissues must favor infection not by making a more favorable medium for the growth of the bacteria, but by injuring the tissue-cells so as to diminish their resisting power. He furthermore injected subcutaneously into one rabbit a given dose of staphylococci in saline solution, and into another rabbit a similar dose in 25 per cent dextrose solution. The second rabbit developed a large abscess, the first developed none. Also, he injected subcutaneously into two rabbits equal doses of a dilute staphylococcus suspension in 12 per cent dextrose; then during four days one rabbit received subcutaneously a Pravaz syringe-full of 12 per cent dextrose, and the other an equal injection of saline solution. The one receiving the repeated dextrose injections developed an abscess; the saline control rabbit showed no abscess. Still another rabbit received intravenously ten syringe-fulls of 10 per cent dextrose solution, and subcutaneously a dose of staphylococcus which of itself would not suffice for infection. The result was "gangrene" of the skin of the infected area. At the close of Bujwid's paper, there is appended a brief note of confirmation by Karlinski. The latter was able with sugar-solutions [strength not stated] and minimal quantities of culture to produce abscesses in 5 rabbits, 2 guinea-pigs, and 5 mice. The sugar-solution is said to increase the local reaction against staphylococcus, for in all five mice there developed small local abscesses without systemic infection, while in 5 control

mice there were two negative results and 3 cases of generalized pyemic infection. Karlinski's results to some extent oppose Bujwid's, since the dextrose in some cases apparently saved the animals from generalized infection. Any harmful effects of the sugar in such experiments are easily explainable as a non-specific osmotic injury.

Lesne and Dreyfus (2) reported that animals show lowered resistance to chicken-cholera infection, or to tetanus or diphtheria toxin, in consequence of sugar injections. The injections referred to were large doses into the peritoneum, again explainable as a non-specific injury.

Nicolas [ref. by Lepine (1), p. 599] found that sugar injected subcutaneously along with staphylococci increases the liability to abscess. The methods were apparently analogous to those of Bujwid.

Grossmann [ref. by Lepine (1), p. 600] is said to have confirmed and extended the results of Bujwid. He found both staphylococci and streptococci attenuated by cultivation in sugar-media. But a culture of staphylococcus or streptococcus, insufficient of itself to cause abscess on subcutaneous injection into rabbits, produces an abscess if the suspension be made in 0.5 per cent sugar solution instead of in physiological saline solution. It is questionable whether the addition of dextrose in such low percentage to physiological saline would have any such effect. The experiments were perhaps done with the dextrose dissolved in water, in which case the injury from the hypotonic solution would explain the results.

IV. *Skin-troubles* are naturally the next complication to be considered, because many of them are of the nature of infections. The conditions most commonly named are furuncles and carbuncles, gangrene of the skin, general or localized pruritus, urticaria, acne cachecticorum, eczema, psoriasis, paronychia diabetica, xanthoma, loss of hair, abnormal flushings, abnormal pigmentations, etc. In the same list for the present purpose may be placed the frequent superficial infections with pathogenic fungi, especially that of oidium albicans in the mouth; and the slight or severe, irritative and infective disorders of the bladder, urethra, and the entire genital region. All of the genito-urinary lesions referred to are known to be due largely or wholly to the presence of sugar. And in the mouth, von Noorden [(1), p. 183] ascribes the frequent occurrence of thrush to the saturation of the epithelial strata

with sugar solution [derived evidently in this instance from the blood, since sugar in the saliva is very rare].

Furuncles or more serious pyogenic infections are notoriously common. Von Noorden (p. 179) finds them in one-tenth to one-fourth of all cases. Naunyn's figures are lower. Staphylococcus aureus is generally found in pure culture; though in some clinics Staphylococcus albus may be a more frequent infecting agent. The part played by sugar in the etiology has been covered in the discussion under heading (III) above. That reduction of the hyperglycemia is the most important measure in the treatment of such conditions is universally recognized. On the other hand, these infections may occur in patients with only slight hyperglycemia, and often at an early stage of the disease.

Itching is a very common symptom which is seldom mentioned by writers without the accompanying suggestion that it may be due to irritation by the excessive sugar. Dryness and impaired nutrition of the skin are sometimes referred to as contributory factors, but they, in turn, are attributed to the abstraction of water from the tissue by the sugar-laden blood. The sugar is thus held responsible for the dryness, scaliness, loss of hair, pruritus, eczema, for the lesions produced by scratching, and the subsequent infection of these, with resulting furuncles, carbuncles or gangrene. All may be improved or cured by a reduction of the hyperglycemia. Naunyn (p. 239) attributes the itching to the irritation of sensory nerve-endings by the sugar-rich blood, in analogy with the itching in icterus and in uremia. On page 240 he speaks of "glycemic dermatoses." Lassar, a dermatologist, expresses the same views as are held by the general writers on diabetes; namely (p. 205), diabetic itching is due to chemical irritation by the sugar-laden blood; aside from the lesions of scratching, furuncles and carbuncles are frequent because the sugar-soaked tissues are a more favorable soil for the growth of cocci, which always flourish better on a sugar-containing medium. Jarisch, also a dermatologist, has published similar opinions. Yet Naunyn (p. 239) records one case in which the itching failed to abate with cessation of the glycosuria. Brayton has published three cases to show that itching, dryness of skin, thirst, and polyuria do not necessarily mean diabetes mellitus, but in these three instances were the signs of diabetes insipidus.

V. *Complications Involving the Nervous System.* — The list of nervous abnormalities includes psychic changes, hysteria, neur-

asthenia, headache, dizziness, weariness and weakness out of proportion to the apparent state of nutrition, lancinating and neuralgiform pains, pains and cramps of muscles, tenderness of skin, muscles or bones, peripheral neuritis, zoster, loss of reflexes, muscular atrophy, mal perforant and numerous trophic troubles, paralyses, epilepsy, tabes (pseudotabes diabetica), encephalomalacia, apoplexy, diabetic hemiplegia without anatomic lesion, convulsions, and disorders of special sense organs, particularly the eye and ear. The importance of nervous disorders in the production of diabetes is generally recognized; there are also opinions in favor of the production of nervous disorders by hyperglycemia. Dawson reported five cases in which glycosuria and insanity were supposed to be related as cause and effect. He mentioned the atrophy frequently found in diabetic brains. The glycosuria in his cases was supposed to be of intestinal origin; but he considered that even secondary glycosuria, if long continued, may act injuriously on the nervous system. Oppler refers to the frequent reports of glycosuria in connection with certain forms of psychic disturbance, especially of depressive character; these were only partially confirmed by Ehrenberg (Monatsschr. f. Psychiatr. u. Neurol., 25, Heft 1) and Tintemann (Monatsschr. f. Psychiatr. u. Neurol., 29, 294); but on the other hand Knauer and Schulz (Allgem. Ztschr. f. Psychiatrie 66, Heft 5) demonstrated glycosuria in a very large number of cases of psychic disorder.

Herter (p. 390) said: "The sugar of the blood in diabetes may rise to 0.8 per cent, and we know that the experimental infusion of glucose solution in dogs may be followed by a marked excitability of the nervous system when the sugar-content of the blood exceeds 1 per cent."

Wilenko (3) reported that intravenous injections of concentrated salt solutions irritate the central nervous system. The effects of concentrated sugar solutions were, in general, similar to those of salts, only somewhat weaker.

Albertoni (1) described changes in pulse-rate and blood-pressure in consequence of giving sugar either by injection or *per os*. The changes are absent after cutting the vagi, therefore depend upon a stimulation of central nervous organs.

Kossa (1 and 3) believes in close mutual relations between sugar and the nervous system. His subcutaneous injections of 1 per cent of the body-weight of saccharose in chickens produced, among other symptoms, incoördination, muscular weakness, and

somnolence which he compares with the prodromes of diabetic coma.

Harley tied both ureters in dogs and then injected dextrose intravenously, the idea being to attain a high percentage of blood-sugar. The injection was at the rate of 2 or 3 g. of dextrose every 2 minutes; the duration of injection was about an hour, and the total dose of sugar was 10 or 12 g. per kilo of body-weight. Small dogs were killed by anything over 10 g., but large dogs bore 12 g. per kilo safely. Nervous phenomena were very marked; twitchings, convulsions, weakness, vomiting, acceleration of respiration up to 50 or even 80 per minute; death in some cases. After a few hours all the symptoms disappeared, the blood-sugar having sunk to or below normal. Harley considered sugar a poison.

VI. *Cataract* is one of the most frequent and characteristic of the pathological changes of the special sense-organs in diabetes. It is a type etiologically and structurally peculiar to diabetes, different from the senile form, and often present in the young. Older diabetics may have cataracts indistinguishable from the ordinary senile type, and there is still some dispute concerning the relative influences of age and of diabetes in such cases.

This was one of the earliest complications regarding which experimental proof of the etiological effect of sugar was sought. Weir Mitchell produced it first in 1860. He administered to frogs relatively enormous doses of sugar, for example, two drams of syrup injected into the dorsal lymph-sac. Cataract could also be produced by sugar in sufficient quantity by mouth. Mitchell found that a sufficient supply of water for the frog to rest in prevented the appearance of cataract, or removed it after it had appeared. Nevertheless, simple drying of the animals, without administration of sugar, in no case produced cataract.

This work by Mitchell was prompted by the previous publications, by Kunde in 1857, and by Köhnhorn in 1858 [see literature by Heubel], who had produced such cataracts in frogs and even in kittens by use of salts, especially sodium chloride. Richardson in 1860 reported cataracts in frogs and fish, caused by keeping them in a dilute solution of sugar. Others have brought about similar lens-changes in frogs and in rabbits by introducing sugar or salts into the conjunctival sac.

A work of classical thoroughness on this subject is that of Heubel (1). The polemic between Heubel and Deutschmann, in the references listed under their names, contributes further details.

Heubel obtained positive results in various animals, including frogs, dogs, cats, and rabbits. Rabbits were the most resistant. All the cataracts were of temporary nature, and he considers them solely osmotic. Some attention may profitably be directed to the long list of substances named by Heubel (p. 131), by means of which he was able to produce artificial cataracts; for almost all the phenomena described by writers as "sugar intoxication" are just as little specific for sugar as were these artificial cataracts. The same phenomena can be produced by suitable quantities of any substance whatsoever, possessing osmotic properties and sufficiently harmless in other respects.

Reference may also be made to Foá and Viterbi, Manea and Ovio, and Pineles. Experiments with phloridzin are obviously beside the mark. It is now recognized that the temporary opacities of the lens produced by salts and sugar are not true cataract, and the former opinion, that diabetic cataract may be due to abstraction of water from the lens by the sugar-laden blood, has been abandoned.

VII. *Acidosis.* — Harley, whose experiments with large intravenous dextrose-injections in dogs after ligation of the ureters have been mentioned, found the blood of these dogs to contain acetone, diacetic acid, and ethyl alcohol. In control experiments, he determined that ligation of the ureters does not cause the appearance of these substances in the blood. He looked upon sugar as a specific poison, and considered that he had proved the derivation of acetone, diacetic acid and alcohol from the sugar itself.

Pavy repeatedly emphasizes the rôle of sugar in the causation of acidosis, and in at least one type of cases he has held the sugar as the sole cause. For example [(1), p. 119]. "In the 'alimentary' case, which is the type to which I am referring, the 'acidosis' is secondary to the sugar. It would not be present if the urine had been maintained in a sugar-free state. The toxic action of the sugar traversing the system from the food, amongst the deleterious effects produced, promotes, as I have before mentioned, the wrong katabolism that gives rise to the formation of the acids concerned in the matter."

Pflüger [(1), pp. 450–53] said of Harley: "These experiments are of the greatest importance. They prove that in a normal animal the mere presence of sugar in the blood occasions a state of the nervous system very similar to that of diabetic coma, and

even the formation of acetic acid and acetone." Pflüger recognized the derivation of the acetone bodies from fatty acids, and considered that in Harley's experiments the hyperglycemia must have occasioned a breaking down of part of the body-fat.

VIII. *Polyphagia, Polydipsia and Polyuria.* — The literature contains numerous expressions in favor of a sequence such as the following. The diabetic is insufficiently nourished because he cannot assimilate sugar. Therefore he eats abnormally large quantities of food in the attempt to satisfy this "tissue-hunger." The food, especially if it contains much carbohydrate, increases the hyperglycemia. The sugar in the blood, possessing osmotic and diuretic properties, withdraws water from the tissues, and stimulates the kidneys to excrete abnormally large quantities of urine. Therefore in the attempt to maintain the normal water-content of his tissues and his blood, the patient drinks abnormally large quantities of water. This view is well supported by the known effects of diet; the symptoms are increased by a diet which increases the glycosuria, and improve or disappear when a suitable diet overcomes the glycosuria. Thirst and polyuria have been reported by authors who have administered large doses of sugar to experimental animals.

Pflüger maintained that in the diabetic dog, polyphagia, polydipsia, and polyuria are the positive signs of partial extirpation, and that they are absent when the pancreas is completely removed. A few others have held the same opinion. Pflüger also laid emphasis upon the irritation of "hunger and thirst nerves" in the abdomen to account for the symptoms in question.

Teschemacher (1) reported cases of diabetes in which the polyuria persisted long after glycosuria had ceased, and other cases of alternations and transitions between diabetes mellitus and diabetes insipidus. Other reports of the same phenomena exist. Von Noorden [(1), p. 126] denies genuine relations between diabetes mellitus and diabetes insipidus, but recognizes cases of the former in which there is polyuria long before and long after the glycosuria, with the low specific gravity and other characteristics of diabetes insipidus. He also refers to experimental pancreatic lesions which have produced polyuria without glycosuria.

The so-called "diabetes decipiens" was described by Peter Frank over a hundred years ago. In this type of the disease, the urine may be normal in quantity despite marked glycosuria and hyperglycemia. Von Noorden [(1), p. 127] considers this type not

unusual, and gives the following data concerning two patients, both free from nephritis.

	Urine quantity, 24 hours.	Urine sugar.	Blood sugar.
1.....	1600 cc.	4.2 per cent	0.34 per cent
2.....	1400–1500 cc.	3.8 per cent	0.25 per cent

Apparently, therefore, other factors than the simple percentage of sugar may determine the presence or absence of diabetic polyuria.

IX. *Renal Complications.*—Lepine [(1), p. 486] asserts that the kidney of a diabetic patient is never strictly normal. The statements of other authors are less sweeping; but all agree that albuminuria is very frequent among diabetics, and a large, wet, hypertrophic kidney is almost the rule in the absence of true Bright's disease.

From the present point of view, the renal complications of diabetes may be considered in two classes.

(*a*) *True Nephritis.*—Among diabetics this is commonest in the form of granular atrophy. It would require considerable imagination to attribute the condition to sugar-intoxication. Students of nephritis have long attempted to produce the disease by feeding or injection of various poisonous or irritating substances, without success. Many diabetics excrete enormous quantities of sugar for the longest periods without nephritis. In numerous diabetics with granular atrophy, the nephritis existed before the diabetes. That diabetes and nephritis are not related as cause and effect, but rather as two expressions of the same or similar causes, is suggested by the relations of alternation and transition that exist between them. Cases of this type are recognized by all writers. Some patients have shifted back and forth between diabetes and nephritis, excreting sugar for a certain period, then albumin without sugar through another period, then the sugar replacing the albumin again, and so forth. A still more common record is that a patient has diabetes with constant glycosuria for a number of months or years, then the condition changes into Bright's disease, and thereafter he can eat starch or even sugar without glycosuria. Some have looked upon this as a favorable termination of the diabetes. But von Noorden [(1), p. 111] finds it a very fatal complication. The glycosuria could be controlled, but the nephritis is beyond help. Vas writes in much the same

spirit, looking upon nephritis only as a harmful complication which in many instances does not stop the glycosuria; and even if the glycosuria stops, it may mean merely an altered permeability of the kidney, for the blood-sugar remains high. Naunyn (p. 213–214) admits that glycosuria may remain permanently absent after the onset of nephritis, but rejects the interpretation that the diabetes is thus cured. He considers that in such instances the diabetes and the nephritis are merely earlier and later manifestations of the same morbid condition, probably arteriosclerosis. By the time the nephritis is well-marked, the patient's general vitality is so weakened that the glycosuria ceases merely as a result of cachexia. He compares the condition to the cessation of glycosuria at a certain stage of carcinoma of the pancreas.

(*b*) The second class of renal complications comprises fatty degeneration, glycogenic degeneration, and simple albuminuria without demonstrated anatomic basis. Nothing is known of their etiology, but they might conceivably be due to the action of sugar.

Fatty degeneration is briefly treated by von Noorden [(1), p. 208]. It is a condition discovered by Fichtner, and represented by fat-droplets in the peripheral portions of the epithelial cells lining the convoluted tubules and the ascending limbs of Henle's loops.

The so-called glycogenic degeneration belongs among the abnormal deposits of glycogen in diabetes, mentioned in Chapter II.

Simple diabetic albuminuria is a benign process, often transient, and stands in no known relation with true nephritis. It is said sometimes to show more or less parallelism with the glycosuria. Pflüger and Pavy both believe that sugar can poison the kidneys. Naunyn (p. 212) says: "The cause of this diabetic albuminuria may be sought in influences of the glycosuria upon the kidney; for it is found only after prolonged existence of high glycosuria, and in some such cases the albumin is seen to disappear when the glycosuria is removed. These influences may be the same as produce the *typical hypertrophic diabetic kidney*, and they may therefore be designated as 'irritation of the kidney by the glycosuria.'" Naunyn excludes the poisons of acidosis as a cause.

Kossa (1), Scott, Underhill and Closson (3), and all who have administered large doses of sugar subcutaneously have reported more or less albuminuria. Vas quotes with approval both Kossa and Stokvis, the latter of whom produced albuminuria by dextrose

given either intravenously or by mouth. Richter likewise quotes Stokvis, and states also that from experiments of his own he can confirm the injurious effect of experimental hyperglycemia upon the kidneys. Wilenko (3) determined that intravenous injections of concentrated solutions of either salt or sugar cause, by purely osmotic action, an altered state of the kidney, in the form of first an increased and then a decreased permeability to sugar.

All these experiments involving single, acute intoxications with sugar are of some interest and value, but necessarily never conclusive for the problem under consideration. This remark applies to all the results claimed by all investigators with respect to the influence of sugar upon infections, upon the nervous system, upon the kidneys, upon the nitrogenous excretion (to be considered below), and in all other phases of the subject. That the effects are not specific for sugar, but are for the most part common to all substances possessing osmotic properties, is not such a very serious objection, because many attribute the alleged injury from sugar in diabetes to its osmotic powers, though some believe in a specific toxicity of sugar. But the conditions at best are not a true reproduction of diabetic conditions. The injuries produced can readily be explained by the *suddenness* of adjustment of osmotic relations demanded of the organism in such experiments. That is why all investigators have overshot the mark, and have obtained within a few hours or even minutes more pronounced symptoms of alleged "toxicity" than any ordinary diabetic patient or animal ever shows. The diabetic organism is probably never called upon to react to anything even faintly approaching the suddenness of the osmotic disturbances produced in these experiments. Though there may be a rapid onset of hyperglycemia after piqûre or pancreas-extirpation, or after a heavy meal of carbohydrate in a diabetic, the conditions are yet obviously different from those created by the intravenous injection of concentrated sugar-solution, or by the oral administration of the enormous doses of concentrated sugar necessary to produce albuminuria. That is why diabetic patients or animals may without albuminuria or nervous symptoms excrete quantities of sugar such that the output of one day, injected subcutaneously or intravenously into a normal animal, would cause albuminuria or nervous symptoms. One may easily observe albuminuria and even hemoglobinuria from injections of sodium chloride or urea or water in amount not exceeding the animal's normal daily out-

put; the reason is obvious. Magnus-Levy [(4), p. 161] says: "The observations of Kossa prove that saturation with normal foodstuffs can actually behave as poisons." It is important to understand that Kossa proved no such thing. It is reasonably certain that the hyperglycemia present sometimes, for example, in fever patients, is not producing "toxic" effects, such as are attributed to the hyperglycemia that follows brusque injection of strong sugar solutions.

X. *Excretion of Calcium, Magnesium, and Oxalic Acid.* — The increased excretion in diabetes of certain inorganic substances, especially sodium chloride and sulphuric and phosphoric acids, depends merely upon the increased quantity of food eaten, especially the quantity of protein. The increased excretion of calcium and magnesium has no such routine significance. Gerhardt and Schlesinger found an increase of calcium parallel to that of ammonia. The calcium excretion is especially high in acidosis. The presence of abnormal acids in the organism supposedly causes destruction of bone-tissue, with the consequent elimination of calcium and magnesium. The behavior of calcium especially may be changed in such a manner that the greater proportion of it is excreted through the urine instead of, as normally, through the feces. In this connection, it may be mentioned that the effects following the injection of large quantities of concentrated salt or sugar solutions in normal animals are by some interpreted as an acidosis, and that such injections cause an increased excretion of calcium in the urine.

Diabetic oxaluria is not so firmly established, but is generally accepted as at least an occasional phenomenon. Cantani [ref. by von Noorden (3), p. 611] believed the increased oxalic acid to represent incompletely burned sugar. Mayer [ref. ibid.] holds the same opinion. According to this view, oxalic acid is one stage in the normal combustion of sugar. Magnus-Levy [(4), p. 145] states that the mother-substances of oxalic acid are unknown. Hildebrandt gave rabbits the tremendous dose of 30 g. dextrose per kilo of weight by stomach-tube. Normal rabbits came through safely. Those fed solely on oats, an "acid" diet, were killed by the dextrose, because, according to Hildebrandt's interpretation, they did not have sufficient alkali at their disposal to neutralize the oxalic acid formed from the dextrose. These oat-fed rabbits could be saved by giving them chalk along with the dextrose. The increase of oxalate excretion produced by

giving dextrose [or glycuronic or saccharic acid, in Mayer's experiments] is much greater than can be produced by other experimental methods. Hildebrandt tested the effects of poisoning with sodium oxalate, and considers them identical with the symptoms of death from dextrose. He concludes that the toxic effects of excessive doses of dextrose are an oxalate poisoning. Magnus-Levy accepts the view that oxalic acid may, at least under abnormal conditions, appear in the urine as a product of the incomplete combustion of dextrose.

Roubitschek examined the urine of fifty diabetics, and found increased oxalate excretion in a third. But in one such case, meat-diet increased the oxaluria, while carbohydrate had no such effect.

XI. *Increase of Nitrogenous Metabolism.* — The uniform findings of Kossa, Scott, Underhill and Closson, and others show that the subcutaneous injection of large quantities of sugar results in a considerable increase of the total nitrogen excretion. The importance of the simple shock to the osmotic equilibrium has been properly emphasized by Heilner. It has been a source of some surprise that sugar introduced parenterally does not spare protein. Some authors have believed or suspected that sugar may behave very differently according to its origin, *e.g.*, whether it arises in the tissues, or is absorbed from the intestine via the portal tract, or is introduced with avoidance of the liver. Benedict and Joslin found no specific increase of nitrogen excretion from ingestion of carbohydrate in human diabetes.

In general, numerous weighty opinions favor the importance of sugar in the causation of various symptoms or complications of diabetes. The injection of large quantities of sugar may produce, besides glycosuria, other phenomena which to some extent, superficially at least, imitate the above symptoms or complications.

2. Influence of Excess of Sugar in Producing Diabetes Itself.

"As long as our ignorance is so great, we shall constantly make mistakes when for the mixtures of food-substances offered to us by nature we attempt to substitute chemical individuals." This sentence was written by Bunge in an article entitled "The Increasing Sugar-Consumption and its Dangers." The consumption of sugar is undoubtedly increasing. It is generally recognized that diabetes is increasing, and to a considerable extent, its inci-

dence is greatest among the races and the classes of society that consume most sugar. There is a frequently discussed, still unsettled question regarding the possible rôle of sugar in the etiology of diabetes. The general attitude of the medical profession is doubtful or negative as regards statements in words. There are not so many positive open accusations against sugar in the etiology of the disease as there are against it in the etiology of all the complications. But the practice of the medical profession is wholly affirmative. Any patient with even an unimportant reduction of the assimilation-limit for sugar, in the absence of any too-obvious cause, will be advised not to overstep that limit. He is never assured that he may go ahead and make himself glycosuric as often as he chooses and that he will suffer no harm in consequence. It is worth while to examine into the evidence, mostly well known, upon which such a universal medical practice is founded, and to define the problem clearly, and then if possible to add some experimental data to the existing evidence.

Diabetes is said to have been first noted in the writings of Celsus in the first century, and first named and partially described by Aretæus about 150 A.D. The sweetness of the urine was first mentioned among European races by Thomas Willis in 1674. In Hindu medical writings of the sixth century the disease was given the name of Madhumeha or "honey-urine." A passage translated by Chunder Bose is as follows. "Madhumeha is a disease which the rich principally suffer from, and is brought on by their overindulgence in rice, flour, and sugar. The patient feels weak and emaciated, and complains of frequent micturition, thirst, and prostration. Ants flock round his urine. Carbuncles and phthisis are its frequent complications." This ancient belief has a point in its favor which modern clinical statements must lack, for it originated before the time of organic chemistry, and there was no way for its authors to know that flour and rice are largely carbohydrate, and that carbohydrate in digestion is converted into the sugar which appears in the urine. This definite incrimination of the principal carbohydrate foods is, therefore, free from preconceived chemical ideas, and is based, if not on pure accident, on pure clinical observation. But Bose himself, with a more modern viewpoint, states that he does not know how much the heavy carbohydrate diet and the gluttony of the Hindus may have to do with the great prevalence of the disease among them; but unless the unknown cause of diabetes is present, a person may

eat gluttonously of carbohydrate all his life and never have diabetes.

Williamson, writing of the geographical distribution of diabetes, notes that the disease is increasing; that it is specially prevalent among Jews and Hindus, and common also in Ceylon, Siam, Tunis, and Madeira. The poorer Chinese rarely have diabetes, but the rich ones, who eat European food and drink sweet wine, suffer from the disease fairly often. Other authors have noted that in India diabetes is much more prevalent among the Hindus, on a vegetarian diet containing much carbohydrate and sweets, than among their meat-eating Mohammedan neighbors. There is printed a discussion on diabetes in the tropics, in the British Medical Journal for 1907, pages 1051–64. The same journal for 1909, II, page 807, has an editorial on the geographical distribution, with a few statistics and speculations. The import of Mitra's article on "Diabetes the bane of Bengal" is conveyed by its title. With these we may close the subject of geography.

Among the authorities on diabetes, von Noorden [(1), p. 54] declares against any relation between the eating of carbohydrate and the incidence of the disease. Naunyn (pp. 157–58) takes a position partly affirmative and partly negative. He stands against the idea that carbohydrate diet increases the incidence of diabetes. But he believes that rich living and the use of alcohol favor the development of the disease, by leading to arteriosclerosis and to heart and liver troubles, and by putting strain on the metabolism which may ultimately lead to its breaking down. He also concedes that, in connection with high living, large quantities of sweet foods and the maltose of beer favor the onset of diabetes. Lepine is unequivocally in favor of sugar as one of the causes of diabetes; heavy eating is an "efficient cause" of the disease; a stinted diet composed largely of carbohydrate is less productive of diabetes than a rich diet of other foods, nevertheless a diet almost exclusively carbohydrate predisposes to the disease; Trappist monks and laborers in sugar-factories frequently become diabetic; beer, cider, and certain wines have a diabetogenic action; alcohol itself predisposes by a two-fold action, one as a protoplasmic poison, the other as a cause of lesions of the liver and pancreas.

A. L. Benedict (2) considers that though some diabetics give a history of excessive eating of sugar or carbohydrates, many non-diabetics are guilty of equal excesses, particularly young girls who live on candy. Supporters of the sugar-theory call

attention to the concomitant increase of diabetes and of sugar-consumption. But if sugar were a cause, diabetes should be more prevalent among the young, especially girls; and a larger proportion of case-histories should show sugar-excess. The products of carbohydrate digestion and metabolism are not toxic, and indigestion generally stops the excess before long.

LeGoff found by alimentary tests that cane-sugar passes easily into the blood, and raised the question whether the prevalent substitution of this sugar for the carbohydrates of the natural primitive diet might have an influence in the production of diabetes.

Bunge's paper was written not concerning diabetes, but to warn against the deficiency of salts, especially iron and calcium, in a sugar-rich diet. Such deficiency might conceivably have an influence toward diabetes. There have been attempts to relate this disease with the ionic physiology of Jacques Loeb. Glycosuria can be produced by intravenous injections of certain salts, especially sodium chloride. Stoklasa observed that an abundance of potassium is associated with active oxidation in certain lower plants, and poverty in potassium is associated with weak oxidation. He considers potassium to be of the utmost importance in carbohydrate combustion, and believes that among the substances which the pancreas gives off to the blood, potassium is an important member. Funck (2) and others have adopted Stoklasa's idea. Large doses of sugar may produce increased excretion of calcium and magnesium, and increased excretion of these substances was mentioned as occurring in diabetes. Stürmer lately reported benefits from a magnesium therapy of diabetes, but has been contradicted by Hirose. Calcium has been brought into various relations with internal secretory organs and abnormalities, and calcium injections inhibit the glycosuria produced by adrenalin.

But the most probable among the possible effects of sugar is a simple overstrain of the assimilative power. Hoffmann [ref. by Naunyn, p. 204] enunciated the dictum, "overstrain weakens, rest strengthens, any damaged function." In the application of this dictum to the diabetogenic influence of sugar, it will be found, on close analysis, that the only point of dispute is whether the word *damaged* shall be retained or not. The two possible views may be considered successively.

A. Normal individuals vary widely in the power of assimilating sugar, and the gradations are so numerous that it seems

impossible to draw an absolutely strict line between the normal and the pathological, or between the mildest diabetes and other forms of glycosuria which are apparently not diabetic. Pavy has insisted that the difference is only of degree; that the mild diabetic differs from the normal person only in the possession of a somewhat lower carbohydrate tolerance. Pflüger considered a distinction between diabetes and other forms of glycosuria impossible. Naunyn has made glycosuria *ex amylo* a distinguishing test for diabetes; but Hofmeister and others have seen glycosuria from ingestion of starch in fasting dogs, and von Noorden [(3), p. 541] and Strauss have reported the same in alcoholics and in influenza and pneumonia patients; and according to von Noorden such glycosuria may partake of the diabetic character. Solis-Cohen calls diabetes a syndrome, and says, "I do not know any definite disease called diabetes mellitus." Funck (2) states that the diagnosis of diabetes means no more than the diagnosis of fever.

In the absence of any radical difference between diabetes and non-diabetic conditions, the assumption of a possible production of diabetes by sugar is logical. Excessive indulgence in sugar admittedly weakens the assimilative power in diabetes; if there is no hard and fast dividing line, a sufficiently excessive indulgence may presumably weaken the assimilative power of individuals in whom this power is normal or slightly reduced. The analogy with other forms of overstrain is also entirely logical. A "weak" digestion is easily upset; but sufficiently improper food for a sufficient length of time will cause indigestion in anybody. On this basis, the ingestion of sugar, if sufficiently excessive and prolonged, might conceivably bridge the gap between the non-diabetic individual with the lowest sugar-tolerance and the diabetic individual with the highest sugar-tolerance; the possibility would be particularly great in an individual possessing strong digestive power with weak assimilative power. In other words, sugar might under certain conditions be an actual cause of diabetes.

B. According to the opposing view, though a practical distinction may be difficult, there is always an absolute theoretical line between a non-diabetic person with even the lowest assimilative power, and a diabetic person with even the highest assimilative power. Schlesinger (1) considers it improbable that the difference between health and a fatal disease is a mere matter of degree of tolerance for a particular food. A. L. Benedict finds

that in practice non-diabetic forms of glycosuria are rare. Lowered tolerance generally means latent diabetes. Barringer and Roper investigated the question of spontaneous glycosuria and alimentary glycosuria (e saccharo) principally from an insurance standpoint. They quote authors who favor the view that there is no fundamental difference between these forms and diabetes. They themselves found that most of the persons who at the first examination had only an "alimentary" glycosuria, in the course of a few years showed definite diabetic tendencies. Abderhalden writes (p. 341): "The fact that the diabetic, whose blood and tissues are saturated with sugar, and who is already greatly injured as regards the economy of energy by reason of the loss he suffers because of his inability to consume sugar, even prepares more sugar from the other nutrients, only to eliminate it eventually as such, shows us that the assumption that diabetes is only a simple derangement of carbohydrate metabolism does not satisfactorily explain the disease. Up to the present time the most prominent symptom, that of glycosuria, has dominated the entire investigation of problems concerning diabetes, and it is very probable that this is the reason why the disease, as a whole, is so little understood."

According to this conception, sugar can never be the actual cause of diabetes. But its importance in the etiology of the disease is not thus excluded. The existence of concealed diabetic tendencies in a considerable number of human beings must be recognized. Latent weaknesses may remain latent, unless the exciting cause is added to the predisposing cause of disease. Analogy may be drawn with the strongly suspected conditions in cancer. Many a person lives and dies with some wart or mole or lump of any kind in which no pathologist could find anything malignant, and it is unthought of and harmless. In other persons under presumably identical conditions, some irritation is added, and frank malignancy is the result. With full allowance for a cancerous diathesis, it seems true that if the man is a chimney-sweep in London he may have his cancer about the scrotum, and if he is a bearded native of central Asia with a tight waist-band he may have it on the abdomen, and if he is a smooth-shaven Occidental he may have it on his face from a razor-cut, and if he is fortunate enough to escape all effective sources of irritation he may escape cancer altogether. It is not unfair to assume that for the person of diabetic diathesis, sugar constitutes just such an irritant. Benedict suggests that the disease should then be

most common among young girls; but the underlying diabetic tendency is more marked in later life. Bose affirms that if the unknown cause is absent, a person may eat gluttonously of carbohydrate all his life and never have diabetes. This is true; and it is also true that a sufficiently strong diabetic tendency will produce the disease whether the person eats sugar or not. But there is presumably a considerable class with only a slight or moderate tendency to the disease. And presumably, if a member of this class is a Hindu he may die in middle life of diabetes, and if he is an Eskimo he may live to senility with never a trace of glycosuria. If he is a poor laborer he may eat freely of starch, and dispose safely of the glucose arising from it, because of the slower process of digestion and assimilation of starch as compared with free sugar, and because of the greater efficiency of combustion in the muscles due to exercise. If he is well-to-do, sedentary, and fond of sweet food, he may, with no greater predisposition, become openly diabetic. The difference is then chiefly of diet. Allowing for nervous and other concomitant influences, this reasoning plausibly explains certain known facts concerning the increased incidence and geographical distribution of diabetes.

The attempt to answer this question experimentally possesses interest not only for diabetes but also for the general subject of internal secretion. Not infrequently in the literature, reference is made to supposed "strain" of internal secretory organs, *e.g.*, "strain" of the thyroid and other functions in pregnancy. But very little is yet known concerning the possibility of "straining" an internal secretory function. Carbohydrate assimilation furnishes a valuable starting-point, for the stimulating substance, viz., sugar, is simple and definite, and in diabetes there is evidence that overstrain of the assimilative function is capable of breaking down that function. The question then is whether the function must first be damaged in some specific manner before it can be broken down by sugar, or whether a sufficiently excessive and prolonged strain may break down even the normal assimilative power. The physiological peculiarities of sugar furnish ideal conditions for the experiment. Disturbances of digestion may be avoided by the method of parenteral injections. The different sugars thus injected are relatively harmless even in large doses. Above all, it is known that dextrose thus administered to a normal animal *must* be assimilated; no matter how large the dose, only a trifle can be excreted, and the remainder must be disposed of

inside the body. It is thus possible to keep animals for long periods in good health in other respects, yet with a continual overstrain upon their dextrose-assimilating power and an almost continuous glycosuria. Also, other sugars, such as lactose and saccharose, imitate to some extent the sugar of the diabetic organism, which cannot be burned. By injections of these sugars, it is possible to maintain a high and continual excess of sugar-molecules in the blood and tissue-fluids, and a continual secretion of sugar-heavy urine, equal to the conditions present in diabetes. Consideration of the effects of sugar in "predisposed" animals must be deferred for several chapters; but the present chapter will concern the question whether normal animals can be made diabetic by prolonged excess of sugar. Incidentally, the other possible effects of sugar may be observed, and especially the possibility of a chronic toxic effect of sugar, analogous to that of mercury, lead, arsenic, etc. Since the opinions and speculations have been so numerous, it is rather surprising that so few attempts have been made to determine the consequences of prolonged excess of sugar experimentally.

Kossa (1) undertook to study the pharmacology and toxicology of sugar, but succeeded in studying only the osmotic effects of large doses of concentrated solution. He used subcutaneous or intramuscular injections, chiefly of cane-sugar in fowls, but extended his work also to dextrose and a few mammals. He observed collapse-phenomena in fowls after injection of 10 g. saccharose per kilo, and repetition of the dose led to death. Autopsy showed acute renal and other visceral changes. Kossa considered the effects of saccharose and of dextrose the same. In any other than an osmotic sense, it is of course impossible for saccharose and dextrose to behave identically in the body. The strength of solutions used is not stated, but they must have been highly concentrated. The concentration would explain the "gangrene" and infection which were the rule in Kossa's animals. Probably also with weaker solutions the collapse-phenomena noted in birds are less marked or absent, for Süssenguth failed to confirm Kossa on this point. Mammals bear the injections better than birds. Kossa found that rabbits bear the daily injection of 5 to 10 g. per kilo of saccharose for 2 to 4 weeks, with no particular symptoms except progressive emaciation. In 3 weeks 21 to 36 per cent of the body-weight may be lost. Dogs show less emaciation. In one instance there was even a gain of weight. But the injections in

dogs cannot be continued as long as in rabbits, because sooner or later abscesses begin to form at the sites of injection, in spite of aseptic precautions. The longest recorded experiment is 26 days, in a rabbit. The other effects of sugar are local irritation, hemorrhages in various parts of the body, albuminuria (more in rabbit than in dog), and very marked increase of nitrogenous excretion. All these effects are brought by Kossa into relation with the symptoms of diabetes. He considered diabetes largely a sugar-intoxication, and compared the diabetic gangrene, infective processes, albuminuria, increased nitrogen output, and even the coma with the effects resulting from his sugar injections. In his latest publication (3) he reaffirms these views. Kossa's experiments have been widely accepted, and have exerted considerable influence on the views concerning sugar-intoxication.

Lucibelli [ref. by Lepine (1), p. 204] repeated Kossa's experiments, using dextrose. When a rabbit was given daily injections of 20 g. per kilo, death soon resulted, with local œdema, parenchymatous renal changes, fatty degeneration of the liver, hyperemia of the lungs, and fatty infiltration of the myocardium. With smaller doses, the rabbits did not die, but they were less resistant than normal to artificial streptococcus and pneumococcus infections. If the dose was not above 4 or 5 g. per kilo per day, the rabbits showed no ill effects. There was even a certain accommodation to the sugar, for the doses could later be somewhat increased without ill effects.

Marrassini (1) studied the islands of Langerhans. Part of his work consisted in giving rabbits subcutaneous injections of dextrose in 20–25 per cent solution, increasing the dose till on the fifth day it was 15–20 g. dextrose, when considerable glycosuria generally appeared. The doses of dextrose were made larger or smaller, as circumstances required, to maintain a satisfactory glycosuria. The rabbits were killed at various periods up to 20 days from the beginning of injections. Other rabbits were given dextrose by mouth. Great variations in tolerance were observed. Hypertrophy of the islets of Langerhans, and transformation of acini into islets, are said to have resulted in these sugar-experiments. Marrassini (3 and 4) gave dextrose to rabbits and guinea-pigs by mouth. Enough was given to cause glycosuria, and the duration of the experiments was from 35 to 70 days. Changes in the adrenals are said to have resulted in guinea-pigs, but not in rabbits. The changes consisted in enlargement of

the adrenals, due to hypertrophy of the cortex; the reticular zone was especially broad. The medullary portion was normal.

These may be classed as the best experiments that have been done in this field. The glycosuria was relatively slight, and the duration short, as compared with the conditions in diabetes. The fact that rabbits and guinea-pigs showed none of the signs or symptoms of diabetes after 70 days of this mild treatment cannot be considered to close the question.

Süssenguth (2), working with rabbits and guinea-pigs, gave daily subcutaneous injections of 5 to 10 g. per kilo of dextrose in 50 per cent solution, increasing from the smaller to the larger dose. The duration of the experiments in guinea-pigs was 1 to 2 weeks; in rabbits 10 days to over 5 weeks. The polyuria, polydipsia, polyphagia, and other symptoms of diabetes never appeared. The animals lost weight steadily, the loss toward the end amounting to 15 per cent. The first injections were absorbed promptly. The later ones formed persistent tumefactions which later came to abscess. "On account of the slower absorption," glycosuria became continuous during this time; whereas at the outset it had lasted for only a few hours following the injection. Glycosuria in the guinea-pigs amounted to 0.05 per cent to 0.2 per cent; in the rabbits, 0.3 per cent to 2.3 per cent. The animals died of sepsis. Albuminuria was not encountered. The lesions described by Kossa were not found at autopsy. A few pigeons were also used, and Kossa's results with chickens and pigeons were not confirmed. Süssenguth concludes that sugar is not responsible for the supposed toxic effects in diabetes.

Süssenguth's work is chiefly of interest as contradicting Kossa's results in birds. The tumefactions reported are attributable to simple infection, not to altered absorption; and the more pronounced glycosuria in later stages presumably corresponds to the weakened condition of the animals.

The most recent work in this field is that of Lucien and Parisot. Every two days, they gave rabbits enough sugar by stomach to produce well-marked glycosuria for several hours. The study especially concerned the liver. After 1 to 4 months of the above treatment, they claim an increased size of the liver proportional to the length of the experiment, and microscopic changes in the liver cells.

The few other researches with repeated injections scarcely apply to the present subject. Mendel and Mitchell injected

saccharose intraperitoneally in a dog for $7\frac{1}{2}$ weeks, but the injections were only "at intervals." The experiments of Weinland and of Abderhalden heretofore mentioned involved only a few repetitions of the injections. Schaps (1) observed "immunity" after sugar-injections in infants, but the injections were few and tiny. The long-continued phloridzin treatment, either of v. Mering or of Lazarus and those who repeated his work, have no application here, because phloridzin does not cause hyperglycemia.

EXPERIMENTS.

In presenting my own experiments, I shall begin with the failures, which may perhaps be instructive.

The first represent a series of rabbits of the same lot, varying somewhat in weight, but as similar as possible in other respects. The experiments were with subcutaneous injections, and were instituted to get a general idea of the tolerance, resistance, and behavior of the animals. The series comprised the following:

Rabbit 31 . . . . . 10 per cent lactose solution.
Rabbit 32 . . . . . 0.85 per cent NaCl solution.
Rabbit 33 . . . . . 10 per cent saccharose solution.
Rabbit 34 . . . . . 10 per cent dextrose solution.
Rabbit 35 . . . . . 10 per cent levulose solution.
Rabbit 36 . . . . . 10 per cent maltose solution.
Rabbit 37 . . . . . distilled water.

Several untreated animals of the same lot served as controls. Injections were given every other day, and each animal received the same volume of solution. The molecular strength was, of course, twice as great for the monosaccharides as for the disaccharides, but the 10 per cent solution is not irritating, and the more ready assimilation of the monosaccharides was taken into consideration; with equal doses they would remain a much shorter time in the blood. Also, during and for a week preceding the period of injections, every animal received 50 g. hay and 70 g. oats daily, and the weight, temperature, and eating were recorded.

The experiment lasted only 16 days. The doses varied on different days, but were identical in the different rabbits; the largest was 150 cc. The animals lost weight, and all died except rabbits 32 and 36. Survival was largely a matter of constitutional strength; no special absence of toxicity in maltose is indicated.

There were no infections, except one abscess toward the end in Rabbit 37, when the animal was already weak. Two points were established. (1) The injury is osmotic. Saline solution is probably less injurious than the sugar solutions; but there is no marked difference between the assimilable and the non-assimilable sugars. Distilled water has the highest "toxicity" of all. (2) The emaciation is due to diminished eating. If the animals eat as they did before the injections, they hold weight. If they come to feel a little unwell and lose appetite more or less, they lose weight accordingly. This is a different matter from what might be imagined, viz., an "intoxication" by the sugar causing the animals to emaciate in spite of normal diet.

These rabbits were evidently of a strain with very low resistance to sugar. But the large sugar-injections in rabbits, reported from European laboratories, *e.g.*, by Hildebrandt and by Fichtenmayer, have not been possible in my experience. For three rabbits of another lot, in apparently good condition, I have the following record:

Number.	Weight, grams.	Subcutaneous injection.	Result.
41	940	150 cc. 10 per cent dextrose solution	Death over night.
42	1875	150 cc. 10 per cent dextrose solution	Temperature, 106°; recovery.
43	1100	150 cc. 10 per cent dextrose solution	Death over night.

There is apparently a wide difference in the resistance of different strains of rabbits to osmotic injury.

In a strong black rabbit weighing a trifle over 2 kilos, I was able to confirm Lucibelli's statement that daily doses not exceeding 5 g. per kilo may cause no harm. After a month of daily injections, this rabbit was as fat and vigorous as at the outset. But this dose does not cause glycosuria. None of my rabbits has ever been able to survive daily doses sufficient for glycosuria for as long a period as three weeks, though infections were absent. The trouble with the rabbit for this purpose is that it has a comparatively low resistance, and an exceptionally high assimilation-limit for sugar.

The guinea-pig is no better than the rabbit. With large doses, the animals lose weight, because they huddle up in a corner and eat little. In addition, the skin is relatively tight, so that suffi-

cient quantities of dilute solution are inconvenient to inject. When concentrated solutions are used, inflammatory changes tend to bind down the skin more tightly then before; special care is also needed against infection.

The rat is a hardy animal, and bears repeated sugar-injections sufficiently well; but it is too small, and results in rats might be of questionable value, owing to the specific peculiarities of the animal. I have the record of one rat which bore safely the subcutaneous injection of 16 g. dextrose per kilo, but died in consequence of a dose of 32 g. per kilo.

The dog is a good animal for the experiment, and has the additional advantage of being subject, like man, to natural spontaneous diabetes. But the tolerance of dextrose is high, and two consequences result. One is, that to keep up a glycosuria with chemically pure dextrose for a sufficiently long time would be too expensive for me. Very small dogs, like Hofmeister's, might be used; but these are the very ones most susceptible to distemper and other troubles. The other consequence is that the large dosage per kilo is hard on the animal. Dogs are strong, and will stand almost unlimited sugar if given a day or two of rest betweentimes. But doses sufficient to cause heavy glycosuria make them somewhat ill, with diarrhea and diminished appetite, and the daily repetition seriously impairs their health.

The ideal animal should have a maximum general resistance and a minimum sugar-tolerance. In this respect, the ideal animal is the cat. Doses sufficient for marked hyperglycemia and glycosuria can be borne indefinitely, even if given both morning and evening. The appetite is unfailing, and diarrhea absent, except with the largest doses. The health remains good. The weight and spirits are retained. The animal bears confinement easily, and the loose skin accommodates any amount of injection desired. Even the temper does not make trouble; for after a few days, a gentle cat sits quietly and receives an injection of dilute sugar solution without any need of restraint.

The following is the single experiment which I have carried through, in which the conditions as respects excess of sugar are somewhat comparable to those of diabetes. There was a month of preliminary observation of an animal chosen out of many as a perfect specimen of a cat. The duration of the experiment, from the date on which the first injection was given to the date on which the cat was killed, was seventeen months. It has not been

feasible to reproduce the long protocol in detail. A summary is as follows.

Cat 15; male; white with yellow markings. A young adult. February 11, received. Well-nourished appearance. Let loose in animal room for observation.

April 13, weight 3705 g. Has been under continuous observation, on full diet. Constantly normal, active, comfortable, affectionate; good appetite; an excellent mouser; shows ordinary behavior in his relations with two or three other cats loose in the room at the same time. Today placed in a large cage. Subcutaneous injection of 10 cc. 20 per cent dextrose solution. No glycosuria.

April 14–24, daily subcutaneous injection of 30 to 50 cc. 20 per cent dextrose solution. Steady increase of weight to 4085 g. on April 24.

April 25 to May 5, daily subcutaneous injection of 80 to 100 cc. 10 per cent dextrose solution every forenoon, and the same dose every afternoon. Constant heavy glycosuria. Good general condition. Steady decline in weight to 3775 g. on May 5, due to slightly diminished appetite and slight diarrhea. On May 4, a blood-count* showed the following:

Reds = 9,800,000.

Whites = 22,400
- Polymorphonuclears, 66 per cent.
- Large mononuclears, 5 per cent.
- Small mononuclears, 17 per cent.
- Eosinophiles, 12 per cent.

May 6–19, subcutaneous injections of 40 to 200 cc. 10 per cent dextrose solution daily. Tolerance lies between 80 and 100 cc. Injection of 100 cc. causes rather heavy glycosuria continuing several hours. Injection of 200 cc. produces intense glycosuria, always ceasing in less than 24 hours.

May 20, weight 3545 g. Starvation begun. Daily subcutaneous injection of 200 cc. 10 per cent dextrose solution. Heavy glycosuria. The experiment continued till interrupted by the condition described in the following excerpt from the protocol.

* Richet's dictionary gives the normal blood-count of a cat as:

Reds = 9,900,000.

Whites = 7,200.

I am ignorant of the normal character or percentage of the different white cells. In the differential count, I merely grouped them according to their apparent resemblance to the types of human blood.

June 5, weight 3250 g. Cat this morning is found showing sudden and unexpected ataxic condition. Tests show that there is no paralysis anywhere. Muscular weakness is also absent; for example, the cat resists removal from cage, and shows surprising strength in his struggles. But as he sits in cage, there is a constant, slow, gross shaking like paralysis agitans; it involves the whole body, but especially the head and neck. It shows the characters of an intention tremor, becoming violent whenever the cat attempts any special act. For example, when offered a mouse, his incoördinate and exaggerated attempts to seize it throw him all about the cage. Attempt to drink causes violent bobbing of the head. Placed on floor, his incoordination makes walking impossible; trying to start in one direction he staggers off in another, and in the attempt to right himself falls sprawling. Consciousness and mentality entirely normal. No sensory changes discoverable. Rectal temperature 99[2]. No injection today.

Drinks 50 cc. milk with difficulty. Refuses meat, but 100 g. fed forcibly.

June 6, weight 3010 g. Condition like yesterday, but cat is weaker. Forcible feeding. Injection of 200 cc. 10 per cent dextrose solution.

June 7, weight 3160 g. Takes milk and two mice willingly; a little meat fed forcibly. Strength a little better; incoördination as before. Injection as before.

June 8–15, daily injections continued as before. Gradual improvement of appetite, strength, and steadiness; by June 15, all ataxia gone; weight 3340 g.

June 16–25, daily subcutaneous injection of 200 cc. 10 per cent dextrose solution. Heavy glycosuria. Urine normal except for sugar. No ataxia. Weight June 24, 3695 g.

June 26 to July 1, no injections. The daily weighings show a more rapid gain of weight than with injections.

July 2, weight 3985 g. Fat, comfortable, normal. No ataxia. Starvation begun, with daily subcutaneous dextrose injections. At first the daily dose was 100 cc. 10 per cent, later it was 10 cc. 80 per cent dextrose solution. Excerpt from protocol.

August 9, weight 2475 g. A.m. temperature 100; p.m. temperature 101[2]. Pupils dilated; marked ataxia; unable to stand; sprawling movements and somersaults on trying to move about his cage. Consciousness retained; but he is somnolent much of time, and acts confused when roused. Muscular strength excellent, as shown by violence of his tumbling and somersaulting. Eats one piece of meat greedily but with difficulty; refuses the rest. The dilated pupils react normally. Usual injection given of 10 cc. 80 per cent dextrose; and a little meat fed forcibly.

August 10, weight 2420 g. Temperature 100[2]. The usual injection of 10 cc. 80 per cent dextrose.

A little better than yesterday, for today he is able to stand and walk very unsteadily. Any excitement that rouses him to action in his cage results in turning somersaults; on the floor mere sprawling results, for his feet cannot get the purchase

on the floor that they get on the mesh of the cage bottom. Refuses meat, but is ravenous for mice. One mouse given him; he seizes it with great difficulty and exaggeration, growls savagely, and turns somersaults about the cage for five minutes continuously in the effort to eat it. Finally, by bracing himself in a corner, he succeeds in devouring it. Dilated pupils and mental confusion still present but less marked. A little meat fed forcibly during day.

August 11, weight 2520 g. Temperature 101^4. 10 cc. 80 per cent dextrose injected subcut. One mouse fed; he succeeds in eating it without somersaults. Takes milk willingly though with difficulty, and is fed some meat forcibly.

August 12, weight 2555 g. Temperature 100^6. 10 cc. 80 per cent dextrose injected subcut. One defecation. Eats a mouse, milk, and fish, but refuses meat. Pupils back to normal. Gaining steadiness, but still staggers drunkenly in walking.

August 13, weight 2635. 10 cc. 80 per cent dextrose injected subcut.

Aug. 14, weight 2700 g. Temperature 102^7. No injection. Steadiness improving. Sleeps nearly all the time, much more deeply than Cat 7* or any normal cat. Effort required to waken him. Eats.

August 15–22, daily subcutaneous injection of 10 cc. 80 per cent dextrose solution. Strength and coördination gradually improved. August 22, weight 3085 g. Normal except for slight distinct unsteadiness of hind legs. Let loose in room, to remain there, so as to give exercise and avoid too long confinement. Peaceable with other cats in room.

August 23 to September 1, daily subcutaneous injection of 10 cc. 80 per cent dextrose solution. Weight September 1, 3495 g.

September 2–9, daily subcutaneous injection of 30 cc. 50 per cent dextrose solution. Blood-count on September 8, reds 9,600,000, whites 12,600. September 9, small incipient abscess opened, and cat given freedom on roof without injections. Weight September 9, 3620 g.

September 9–16, on roof free.

September 17–20, loose in room without injections. Still catches mice.

September 21, weight 3535 g. Placed in metabolism cage with empty bladder, and nitrogen analyses begun, for periods with and without dextrose injections [see Chapter IV]. Diet 200 g. lean meat daily, always eaten promptly. Cat in excellent condition, but hind legs definitely unsteady.

November 1, weight 4260 g. Temperature 101^8. Metabolism experiment ended. Most of month of November was occupied with giving of dextrose by mouth, in various quantities and per-

* Cat 7 was a similar animal, which served as control from May 20 to her death on August 10. She was treated in all respects like Cat 15, except the dextrose injections.

centages of solution. Nothing satisfactory was established concerning the animal's tolerance, on account of the readiness with which he vomited; and even when vomiting was avoided, the diarrhea resulting from the sugar was troublesome. Mild glycosuria during much of the time.

November 30 to December 4, daily subcutaneous injection of 20 cc. 20 per cent dextrose solution. No glycosuria.

December 5, weight 4030 g. In the following days, attempts were made toward maintaining alimentary glycosuria by feeding little meat and much milk to which lactose was added, but the results were unsatisfactory on account of indigestion with diminished appetite and diarrhea. Return to meat diet brought weight up promptly. Excerpt from protocol.

December 22, weight 4520 g. The cat is very strong, fat, comfortable, but lazy, more somnolent than a normal fat cat, and unwilling to be disturbed. His fur is heavy and luxuriant, but he neglects the care of it. Though young, he now presents the appearance of a very old, even senile animal; but his muscular strength is surprising. The unsteadiness in walking has increased somewhat, and his swaying is now very noticeable. Climbing is difficult, and falls not uncommon. He avoids all but the easiest jumps; cannot jump on to a table, and if forced to jump off a table, he lands with a sprawl. Another notable change is that other cats somehow regard him as a strange creature; their intense dislike of him is very different from their behavior toward one another, and from their former behavior toward him.

Many of the cats have suffered from cat distemper or "snuffles" lately, and now this cat shows the symptoms. The case turns out a severe one, complicated with purulent conjunctivitis and corneal ulcers. But he is almost the only cat to keep a fair appetite through everything, and his weight never drops below 4 kilos. During the height of the disease, dextrose injections were considered inadvisable.

January 12, weight 4550 g. Is practically well except for ugly ulcer of right cornea. Large appetite. Daily subcutaneous injections, increasing from 20 cc. 20 per cent dextrose to 20 cc. 50 per cent dextrose.

January 22, weight 4665 g. Acts very sick and unsteady. Injections discontinued.

January 24, weight 4370 g. One injection.

January 27, weight 4375 g. Improved, but very unsteady.

February 9, weight 3930 g.

February 14, weight 4100 g. Right eye is nearly well, but unsteadiness is more marked. Cat cannot catch a mouse unless shut up where it cannot escape.

February 27, weight 4480 g.

March 3, weight 4530 g. Urine always normal.

March 8, weight 4320 g. Excerpt from protocol.

During the past days, the cat's behavior has been carefully observed. He is markedly unsteady in all four legs, and not only staggers in walking, but even in standing shows jerking and quivering of muscles in the effort to maintain equilibrium. Yet in tests of simple strength, he is the strongest cat in the laboratory. Sexual instinct is entirely absent; he shows no interest in a female in heat; and the female, which welcomes a normal male, shows only the most intense rage or fear at the approach of Cat 15.

Mental changes are now sufficiently marked to warrant the name insanity. Toward persons the cat is perfectly gentle, very stupid, obstinate, unwilling to be disturbed. He is stupidly greedy for meat and milk, but when shown a mouse, living or dead, he acts as if he did not recognize it, and never kills or eats one — a great change in such an excellent mouser. He appears abnormally fat, decrepit, senile. The character of his cry is changed; instead of a mew, it is now a sort of yell.

His principal alteration is toward other cats. As soon as uncaged, he starts slowly and quietly for the nearest cat. Irrespective whether it is male or female, young or old; irrespective whether it is peacefully sleeping or prepared for battle, his attack is the same. He never spits, or growls, or strikes with his claws as other cats do, and as he used to do. He strolls carelessly forward as if with no special purpose; when at close range, there is one savage clumsy rush; he and his opponent go sprawling together, all four of his paws hugging the other cat, and his teeth buried as deeply as possible in the other's body, in the attempt to kill. If he were not so hopelessly clumsy and incoördinate he might do serious damage; as it is, the other cat instantly escapes and runs as if for its life, pursued with more energy than speed by Cat 15. Savage back-yard tomcats much larger than himself, ready and eager to fight, after one experience with his maniacal attack are forever after in utmost fear of him.

April 1, weight 4485 g.

April 3, weight 4520 g.

April 8, weight 4560 g.

April 13, weight 4450 g.

April 26, weight 4460 g. Bladder emptied by pressure, and 120 cc. 10 per cent dextrose solution injected subcutaneously.

April 27, weight 4520 g. Urine since yesterday 80 cc., sugar-free.

May 11, weight 4320 g. A sinus in the tail is discharging pus; cause unknown.

May 24. The cat is doing rather badly, and the sinus is worse rather than better. Examination shows dead bone at bottom of it. Under ether, tail amputated near base. Evidence is that the trouble started from an injury, probably a bad fall or some other result of the animal's extreme clumsiness.

June 1, weight 4080 g. Healing of tail-wound excellent.

June 10, weight 4310 g. Subcutaneous injection of 140 cc. 10 per cent dextrose solution. No glycosuria.

June 23, weight 4400 g. Temperature 101^6. Subcutaneous injection of 170 cc. 10 per cent dextrose solution. No glycosuria.

July 7, weight 4520 g. Temperature 101^4. Subcutaneous injection of 180 cc. 10 per cent dextrose solution. Very slight glycosuria.

August 11, weight 4490 g. Not fed today. Bladder emptied at 10:45 a.m., and injection given of 150 cc. 10 per cent dextrose solution. At 12:45, cat was etherized and bladder emptied, yielding a few cc., sugar-free. From left carotid was taken 24.1 g. blood. Blood-sugar = 0.539 per cent. Wound closed aseptically. Healing good. There was no glycosuria.

September 12, weight 3800 g. Still preserves all his former peculiarities, but is less strong. Sugar-puncture attempted under ether. Trephine slipped, wounding brain dangerously. Two punctures were then done; cat immediately died and was immediately autopsied.

Autopsy.

Obese animal. Large quantities of fat in all the usual locations. Splendid musculature.

Heart. — Gross and microscopic, normal.

Lungs. — Gross and microscopic, normal.

Thyroid. — Gross and microscopic, normal. Follicles full of colloid.

Liver. — Gross appearance normal. Weight 105.7g. Microscopically normal; fatty infiltration within normal limits. *The entire organ treated with KOH and extract concentrated to small volume shows complete absence of glycogen.*

Spleen. — Weight 10.6 g. Gross and microscopic, normal. Malpighian bodies prominent.

Pancreas. — Weight 7.8 g. Small, but normal in gross appearance and consistency. Microscopically normal. Acini uniformly full of normal secretion. Islets few rather than many; but normal in size, number, and appearance.

Kidneys. — Combined weight 44.8 g. Gross appearance small and dry; capsule strips easily; medulla normal; cortex slightly yellow. Microscopically, normal glomeruli; occasional fat-droplets in the cells of the cortical tubules; a few casts.

Adrenals. — Combined weight 0.5 g. Small; chrome staining deficient. Sections show cortex normal; in the medulla, a few cells approximately normal, but *the great majority pale, vacuolated, pathologically poor in cytoplasm, and devoid of granules.* See Figure 1.

One *testis* and *cord* atrophied till the fibrous remnants are found only after careful dissection. The other, very small and hard, grates on cutting, apparently composed of fibrous tissue. Epididymis likewise fibrous and its canal obliterated. No microscopic examination.

Prostate. — Gross and microscopic, normal.

Sections of a *rib* and adjoining *intercostal muscles* near the cartilaginous junction show normal structure of bone, marrow, and muscle.

Hypophysis. — Gross and microscopic, normal.

Nervous System. — Dissected out and saved in formaldehyde. Gross appearance everywhere normal. The cerebellum and medulla show the wound made by the trephine; in addition, two well-placed punctures in the floor of the fourth ventricle. Tissue for microscopic study was taken from the cervical and lumbar enlargements and the mid-thoracic region of the spinal cord. The cord was fully normal as respects both cells and nerve-tracts. The nerve-roots lying beside the cord at different levels were also normal. Peripheral nerves encountered in the study of various tissues appeared normal, and the Pacinian corpuscles found in the pancreas were normal.

Urine in bladder, amber, acid, sp. gr. 1055, sugar and albumin negative.

Discussion.

The questions regarding nitrogen excretion and also obesity will be considered in the next chapter. The following points may be noted here.

1. The urine record was carefully kept, except during the periods of freedom. Glycosuria was present for a large part of the time, and during the period of heaviest injections was constant and intense. The urine remained constantly free from albumin, bile, acetone, and diacetic acid.

2. There was no marked or characteristic alteration of the blood-count. The count taken on May 4, during the early period of maximum injections, showed the red cells practically normal. There was a leukocytosis, but very likely the subcutaneous injection even of distilled water might cause some leukocytosis. In the

count taken on August 8, the red-count was a trifle low, and the white-count a trifle high.

3. Most of the organs were found fully normal at autopsy. In particular, the pancreas was normal in all respects. The thyroid and hypophysis were normal. Nothing was found in the nervous system to account for the nervous symptoms. The pathological findings may be summarized as exhaustion of the adrenal medulla, absence of liver-glycogen, and atrophy of the testes. The change in the adrenals was not that described by Marrassini, in the cortex. The cortex was fully normal, but the medulla showed the picture of extreme exhaustion. Though the animal died in consequence of Bernard puncture, it seems improbable that any such change as this could be produced when death was practically instantaneous and when the autopsy followed immediately. Unfortunately, it is not possible to state with certainty that the atrophy of the testes came on during the dextrose injections. Though there was a month of preliminary observation, the examination did not include palpation of the testes. Therefore the only basis of judgment is that spontaneous testicular atrophy in a young male cat is rare, and that the animal's general behavior originally was that of a normal male, while later his behavior was greatly changed. As this was the only animal subjected to such treatment for such a length of time, no positive anatomical conclusions will be attempted.

Other conclusions from the experiment must also be drawn with caution. The negative conclusions are the most certain, and may be stated as follows.

I. Long-continued hyperglycemia does not cause diabetes, nor lower the dextrose tolerance.

II. Long-continued hyperglycemia does not cause in a normal animal certain complications of diabetes attributed by writers to sugar-intoxication. Namely, it does not cause the following conditions.

1. *Lowered Resistance to Infection and Delayed Healing of Wounds.* — The cat passed safely through feline distemper, and underwent a number of minor operations, as for taking blood, and the amputation of an injured tail. Wound-healing was perfect. The one or two abscesses that resulted in the course of the injections were resisted in the best possible manner; for normal cats sometimes die from such abscesses. The best test of resistance is that the injections were all given by plunging the needle through

the unsterilized, hair-covered skin. Opportunity was thus afforded for the carrying by the needle of infectious material into the very areas that were to be for some hours saturated with sugar-solution. The persistent absence of infection under such conditions is the best evidence.

2. *Skin Troubles.* — The cat retained a heavy coat of fur, though in the later stages he failed to keep it sleek. He was exposed to the infectious skin diseases of cats, from new animals entering the laboratory. Other cats under the same conditions sometimes contracted these diseases. This cat happened to remain free. Pruritus was not present. Cats with itching skins easily make the condition known by scratching and rubbing; and these symptoms were not present.

3. *Cataract* was absent. Sight and hearing were apparently perfect.

4. *Acidosis* was absent, as already noted. The sleepiness of the cat was nothing like coma.

5. *Polyphagia, polydipsia, and polyuria* were never present.

6. *Albuminuria* never appeared, notwithstanding the long period during which the kidneys were supposedly "irritated" by considerable percentages of sugar in blood and urine.

The negative findings would appear to be fairly convincing. But in attempting to draw positive conclusions, conservatism is necessary, because we are dealing with only a single animal. Controls were not altogether wanting, as will shortly appear. Nevertheless, really adequate controls did not exist, and allowance must inevitably be made for possible idiosyncrasy or possible spontaneous disease in this individual animal.

In one respect, controls were abundant. That is, the conditions observed were not due to long confinement, diet, or other influence of the general surroundings. There were plenty of cats in the laboratory, some of them for long periods; and some of them were confined more closely than Cat 15. Care was taken to give him as much freedom as practicable.

Spontaneous disease as an explanation of the condition is, at least, highly improbable. Part of the picture certainly cannot be accounted for on this basis. For example, there is no known disease that will double an animal's sugar-tolerance, or abolish the liver-glycogen of a fat, well-fed animal.

Attempts at positive conclusions had better be expressed first in the form of questions.

1. May long-continued dextrose-injections double the dextrose-tolerance?

2. May they cause complete disappearance of liver-glycogen?

3. May they cause nervous disorders, namely, impairment of muscular coördination and of mentality?

4. Are any of these effects specific for dextrose, or may other sugars or related substances behave similarly?

1. May long-continued dextrose-injections double the dextrose-tolerance? This first question is the easiest to answer, and an affirmative answer is almost certainly correct. The earlier injections demonstrated the tolerance at this time. For example, on April 25, one injection of 8 g. dextrose in the early forenoon, and another of 8 g. the last thing in the afternoon, caused pronounced glycosuria. On May 10, a single dose of 8 g. caused no glycosuria. But on the following days, doses of 10 g. resulted in heavy glycosuria. On September 4, a specimen of urine after injection of 15 g. showed heavy reduction. By October, the tolerance had risen perceptibly, for doses of 11, 12, and 13 g. caused no glycosuria, and a dose of 15 g. caused glycosuria of only 0.9 per cent. By the next June, the tolerance had risen so that, on June 23, an injection of 17 g. dextrose caused no glycosuria; and on July 7, the limit was ascertained when an injection of 18 g. evoked only a trace of glycosuria. This high tolerance was observed at a time when the cat had been relatively free from sugar-injections for a considerable period. That is, the condition was permanent. Objections may be ruled out as follows:

(*a*) Confinement does not alter a cat's sugar-tolerance, as my experience has demonstrated.

(*b*) Obesity does not alter a cat's sugar-tolerance, as was shown in Chapter I.

(*c*) Intercurrent disease ordinarily lowers sugar-tolerance. While some unknown disease cannot here be ruled out experimentally, it is at least improbable.

Perhaps the strongest evidence that the increased tolerance was due to sugar is presented by the blood-analysis of August 11. No normal cat remains free from glycosuria with a glycemia of 0.539 per cent. What was changed in this cat, therefore, was what Liefmann and Stern call the "external tolerance." That is, the kidneys were less permeable for sugar than normal. Whether what Liefmann and Stern call the "internal tolerance" was in-

creased is not known; the hyperglycemia might have been compared with that of a series of normal cats after the same dose, but this was not done. It may be considered certain that they would show at least an equal percentage. The apparent diminution or loss of the glycogen-storing power of the liver might be supposed to correspond to a diminution of the actual utilization of sugar. But the very large dose utilized seems sufficient proof that the power of the tissues to withdraw sugar from the blood was at least normal.

2. May long-continued dextrose-injections cause complete disappearance of liver-glycogen? The discussion here may start with two facts. First, glycogen was absent. The extract of the entire liver gave no reaction either at the outset or after concentration. Second, the attempted sugar-puncture had presumably nothing to do with the condition. Death was practically instantaneous, and the first thought was of the liver, which was immediately cut up into boiling water. Other cats fed on horse-meat have had livers rich in glycogen, and no reason is known for such a highly unusual finding in a fat, full-fed animal. The liver was not fatty, so that explanation is excluded. Schwarz found the livers of epinephrectomized rats to be glycogen-free. Kahn and Starkenstein have modified the statement to the effect that the livers contain only traces of glycogen. The exhaustion of the adrenal medulla and the absence of glycogen from the liver may perhaps, therefore, be correlated.

The experiment was attempted on the supposition that the liver would be glycogen-rich, and in the hope that the piqûre would produce the usual effects. If glycosuria appeared, it was intended to examine the blood for sugar, in the expectation that the percentage would be found lower than on August 11, and that thus an effect of piqûre in increasing the sugar-permeability of the kidney would be demonstrated. The experiment could not have succeeded because of the absence of glycogen, and the fatal accident was therefore fortunate. It is unfortunate that examination of the muscles for glycogen was not made; for absence of glycogen from the entire body would have been a particularly interesting finding.

From the standpoint of theory, several suggestions are possible. A relation between the glycogenic function and the adrenal medulla, through adrenalin or some other secretion, may perhaps

be indicated. Normally, large dextrose injections cause an abundant formation of glycogen; and it is conceivable that a long-continued excessive stimulation of the glycogenic function might cause it finally to fail. It would be interesting to know whether such an animal can form glycogen from levulose, and whether an animal treated with sufficiently prolonged injections of levulose can form glycogen from dextrose. This experiment, together with the well-established findings in epinephrectomized rats, may render improbable the opinion that diabetes consists in a failure of the glycogen-forming functions; for here the glycogenic function is in default, but there is no diabetes.

Because of the theoretical interest, it is to be hoped that such experiments may be repeated in a larger number of animals. It seems probable that commercial glucose may serve the purpose as well as the pure sugar, though a control experiment might be necessary to assure the fact. A properly trained laboratory helper could give the injections, since infection with a dilute sugar solution is easily avoided. It is to be noted that Cat 15, in addition to dextrose injections, passed through two starvation periods, which might have had some effect. There are some points of interest in extending the experiments to other assimilable sugars besides dextrose and to other species besides cats.

3. May long-continued dextrose-injections cause nervous disorders, namely, impairment of muscular coördination and of mentality? The evidence presented and to be presented shows with reasonable probability that the nervous and psychic abnormalities of this cat were due to the treatment to which he had been subjected. The condition itself might almost be called "paretic dementia," if that term did not have its present clinical limitations. It gives some apparent experimental justification for views, like that expressed by Dawson for example, that long-continued hyperglycemia, irrespective of the origin, may injure the nervous system. It could hardly be considered surprising that a prolonged abnormal composition of the blood and tissue-fluids should produce injury somewhere; and it is to be expected that the nervous system would prove most vulnerable. It may be of some theoretical importance that in this cat a metabolic derangement gave rise to a condition that might be called insanity, and that no organic lesion was found to account for this nor for the deficient muscular control.

Nevertheless, it seems unjustifiable to attempt to bring these findings into relation with clinical glycosuria or diabetes, for the following reasons.

(*a*) In diabetes, the tissues are flooded with dextrose which they cannot use. In an animal like Cat 15, the tissues are flooded with dextrose which they are compelled to use. The distinction may be important; and a derangement of metabolism might more probably be produced in the latter than in the former case.

(*b*) There are human patients, such as the one described by Kleen, who may be intensely hyperglycemic and glycosuric for as long as twenty years. If hyperglycemia causes nervous disorder, such patients should show it.

(*c*) In an animal such as Cat 15, there is importance not only in the presence of the sugar, but in the fact that it is *injected*, and that an osmotic injury is thus produced. In clinical diabetes and glycosuria, no such sudden osmotic adjustments are demanded, and the chance of injury is correspondingly less.

Clinically, glycosuria may be the result of nervous disorder. But in cases where glycosuria may be suspected as the cause of the nervous disorder, it would seem more probable that the two conditions are unrelated, or that some deeper metabolic disturbance gives rise to both the glycosuria and the nervous disorder.

An adequate control for the experiment with Cat 15 is lacking. A number of partial controls contribute more or less information. There may be a question whether the effects produced are due to an idiosyncrasy of this one cat, or of the cat species. Furthermore, in addition to glucose-injections, this cat was subjected to one other experimental condition, namely starvation. The nervous disturbance appeared at the close of the first fasting experiment, and disappeared not long after resumption of feeding. It remained absent till toward the close of a second fasting experiment, when it reappeared. The further progress of the condition took place in the absence of starvation. It is therefore desirable to know whether dextrose alone or starvation alone can produce such effects, or whether starvation plus dextrose is necessary. Also, must the dextrose be given subcutaneously, or will oral administration serve the same purpose? Also, what are the influences of age, sex, and a variety of other factors? For convenience, these numerous questions will be grouped as follows:

A. The question of the effects of sugar alone.

B. The question of limitation to the cat species.

C. The questions concerning idiosyncrasy and other miscellaneous influences.

A. The Question of the Effects of Sugar Alone.

This question must be left without any complete answer. An answer would involve giving to another cat injections like those of Cat 15, for an equally long period, and without starvation or other extraneous influences. There have been both dogs and cats that have received injections of various sorts for periods of six months to a year, but these injections were in connection with other work, and were only intermittent, not daily. There have been other animals started as controls to Cat 15, but circumstances prevented a sufficiently long continuance. Cat 23, for example, received large daily dextrose injections for two months, without visible effect. It may be questioned whether the use of very large injections two or three times every day might shorten the required duration of the experiment. Apparently the dosage used during the most active period of treatment of Cat 15 cannot be much exceeded. Doses that are too large will merely cause acute illness, instead of the slow metabolic changes, with retained weight and general health, which are desired.

B. The Question of Limitation to the Cat Species.

No intentional experiments in this direction were performed. Reference may be made to Dog 18 on July 7 and the days following. The dog had been in the laboratory about 8 months, and had been used for various metabolic experiments. She had been through one starvation period, and one phloridzin period. She had received twenty-five injections of various sugars, many of the doses small, others as large as 15 g. per kilo; they were scattered through the 8 months, not given continuously. The dog was in perfect flesh and spirits, and nothing was noticed definitely before the injection of July 7. On that date, a large subcutaneous injection of lactose (close to 15 g. per kilo) brought on symptoms rather acutely. They were not due to overbalancing the animal by the masses of subcutaneous fluid, for there was abundant opportunity to observe the effects of large injections previously

in this and other dogs. Moreover, the condition was just as pronounced on July 10 as it was on the day of injection. There were no mental changes, no loss of sexual inclinations, no change in behavior toward persons or other dogs, no changes of pupils or other reflexes, no impairment of muscular strength or general spirits; nothing but the ataxia. The dog was full of life and delighted to be out of her cage; but every time she tried to make a little turn or sudden movement on an ordinary floor she went sprawling. On the graveled roof she kept her legs better, but could not guide her movements. In trying to start straight for a given point, she would go drifting off on a diagonal, and had to tack like a ship to reach her destination. She went downstairs chiefly by falling down. In trying to go upstairs, it was evident that she was using her ordinary method, but her feet simply did not go as high as she expected them to go; therefore they struck against the edge of the step, and she took a tumble. After some experience, she learned to compensate; that is, she took each step by means of an exaggerated jump, which landed her safely on the step. But after half a dozen steps, haste or forgetfulness might make her omit the usual high jump; then her paws tripped on the edge and she rolled down a few steps. By eager floundering she always arrived finally at the top. On July 10, she was given freedom on the roof, with the ataxia still prominent. It slowly diminished, and by the end of two weeks was entirely gone. The dog showed no sign of it when caged again on July 31. A large dose of dextrose by mouth (15 g. per kilo) on August 5 caused no sign of ataxia.

It appeared that this dog might by suitable injections have been made permanently ataxic. But other work precluded the experiment. The experience makes it somewhat probable that the ataxia observed in Cat 15 was not an idiosyncrasy of that individual nor of the cat species. Furthermore, it may be noted that it was a large dose of lactose, not dextrose, which brought out the symptoms.

C. Questions Concerning Idiosyncrasy and Other Miscellaneous Influences.

These have been grouped, for the purpose of considering them in a special section by themselves, under the following title:

Starvation Ataxia of Cats.

The cases will be presented in two divisions; first the positive series, second the negative series.

Positive Series.

Cat 19; female; three-fourths grown; weight 1400 g.

Dextrose was given by mouth during starvation, May 23 to June 1, in divided doses distributed through the day. The total for each day varied from 70 cc. 10 per cent solution to 70 cc. 25 per cent solution. The urine sometimes contained sugar, sometimes not. On June 1 there was extreme ataxia and mental confusion, with fair general strength. The animal recovered on feeding.

Cat 59; female; weight 3 kilos.

This animal received 2 g. per kilo of dextrose subcutaneously during the greater part of a starvation period of 26 days, without ataxia. Then, though she was becoming rather weak, a dose of 6 g. per kilo brought on the ataxia within 24 hours. The autopsy findings will be considered in a later chapter. It is sufficient here to say that there is no anatomic change characteristic for the ataxia. The high figure of 0.85 per cent for the blood-sugar is noteworthy. Still more so is the large quantity of liver- and muscle-glycogen present. The ataxia, therefore, does not depend upon a loss of the glycogenic function.

Cat 57; female; weight 3175 g.

December 5–23 was a period of plain starvation. December 24–28, starvation continued with daily subcutaneous injection of 3 g. dextrose per kilo. On December 28 incoördination was present; on December 29 it was extreme.

An attempt was then made to test the relations with tetany or similar states. The symptoms are apparently not identical with those of tetany. But the parathyroids have been supposed to stand in relation with sugar metabolism, and the nervous over-excitability of tetany parathyreopriva is suppressible by calcium. Also, large sugar-injections are said to increase calcium excretion, and it is conceivable that an impoverishment in calcium through prolonged starvation might give rise to nervous symptoms. Accordingly, on December 29, 1 g. calcium chloride was injected intraperitoneally and 1 g. subcutaneously, in 2 per cent solution.

Within an hour there was a convulsion, collapse, and death. The cat had shown evidences of strength enough to live two days at any rate. Acute death has not been seen in any other animal at this stage, and the result was presumably due to the calcium, at a time when only part of the dose could have been absorbed.

Cat 69; female; weight 3400 g.

This cat, in a starvation period from February 13 to March 1, showed no ataxia. After two weeks more of starvation, with addition of subcutaneous injections of commercial glucose (100 cc. 10 per cent solution) typical ataxia developed. Commercial glucose, therefore, apparently acts like the pure sugar.

On March 19, starvation began again. The weight at this time was not quite as high as at the outset of the first experiment, and the fast could not be continued quite as long. Glucose injections were given as before, and the starvation continued to the last day possible without forfeiting life, but ataxia remained absent. An animal may therefore show ataxia in one starvation-period and not in the next.

Cat 58; female; weight 3340 g.

In the case of this cat, a fasting period of 11 days (December 5–16) with dextrose injections of 3 g. per kilo produced no ataxia. After recovery, a second fasting period of 17 days (December 25 to January 11) without dextrose gave rise to fairly typical ataxia. This case is important as being the only one in which anything like ataxia occurred in the absence of dextrose. There may be some question whether the dextrose injections during the first fasting period had in any way sensitized the animal's nervous system, so as to cause effects in the second fasting period.

Two more points are noteworthy. One is that an intraperitoneal injection of adrenalin (2.1 cc. = 1 mg. per kilo) on January 11, at the height of the ataxia produced no unusual effect of any kind. The glycosuria was well-marked, the percentage being very high but the total sugar-excretion very low (urine 15 cc., dextrose 7.3 per cent), as proper in a cat that has fasted 17 days. There was no effect upon the cat's nervous condition for better or for worse. It may be remarked in this connection that Loewi's test of adrenalin-mydriasis was tried in animals whose pupils were not already dilated, and was found negative during the ataxia, just as in normal animals.

The second point to be noted is, that since this cat showed

ataxia without dextrose injections, an attempt was made to refer the phenomenon to the mere nutritive condition. The cat was therefore subjected to repeated starvation periods without dextrose, in the attempt to make the ataxia persistent. There were five of these fasting periods besides the two previously mentioned, making seven such periods in the cat's entire history. The attempt had finally (May 10) to be given up as a failure. It was possible for some time to maintain an unsteady condition of the hind quarters, which seemed out of proportion to the general strength and nutrition. But this was not the true ataxia that has been described; and finally even this weakness of the hind quarters disappeared. It is concluded that the marked ataxia of Cat 15 could not have been due to the two starvation-periods which he passed through.

Negative Series.

Dogs. There have been something above twenty starvation experiments performed with dogs for various purposes. They have been longer and shorter, with and without injection of various sugars. No fasting dog has ever shown the slightest symptom resembling those described for cats. The brief positive result with Dog 18, without fasting, has been stated. But another animal, namely Dog 21, went through a very similar course of treatment, including periods of fasting, phloridzin, and sugar injections, and never showed any nervous disturbance.

Several guinea-pigs, rabbits, and rats have also been starved, some of them to death. Some received sugar injections, and a few guinea-pigs received dextrose by mouth. The records will mostly be found in the next chapter. There was no sign of any nervous symptom at any time.

There have been fully fifty starvation experiments with cats, mostly on different individuals, and with and without various sugars. Many of the protocols will be mentioned in the next chapter. There have been no positive results except those already reported. The percentage of positive cases, however, is not so small as might appear from these facts, because a number of the negative experiments were altogether too short to permit expectation of any positive result. In the absence of any accurate basis of comparison, it is impossible to state any ratio between positive and negative cases. It is possible that the proportion of positive cases may be found to be small. The following instances may receive special mention among the negative experiments with cats.

Cat 76 was a young, barely-grown female, subjected to three fasting periods of one to two weeks duration. In the last period, dextrose was given subcutaneously. In this instance, three fasting periods failed to produce any summation of effects as respects ataxia.

Cat 7 was a female about the size of Cat 15, chosen to be a control for him. She passed through the two starvation periods with him, and died at the close of the second fast. There was no sign of ataxia.

Cat 36 was starved to death while receiving injections of physiological saline solution corresponding in volume to the 10 per cent sugar solutions of the other cats. No ataxia.

Cats 27 and 29 were starved to death while receiving daily subcutaneous injections of 3 g. dextrose per kilo in respectively 10 per cent and 80 per cent solution. No ataxia.

Cat 71 under similar conditions received 10 g. commercial glucose daily. No ataxia.

Cats 32 and 39 received daily injections of 3 g. saccharose per kilo, in 10 per cent and 80 per cent solution respectively. The former was starved to death, the latter to the verge of death. No ataxia.

Cats 18 and 43 were starved, one to death, the other to the verge, while receiving subcutaneously lactose 3 g. per kilo, in 10 per cent and 80 per cent solution respectively. No ataxia.

Cat 30 was starved to death while receiving daily subcutaneous injections of cottonseed oil. No ataxia.

Cat 47 underwent a starvation period while receiving 3 g. per kilo of starch by mouth daily. No ataxia.

Cats 46 and 47 passed through starvation periods (November 22 to December 10) while receiving large doses of thyroid tablets, with and without subcutaneous dextrose injections. No ataxia.

Cat 46 later passed through starvation periods, with and without dextrose injections, after extirpation of most of the thyroid. No ataxia.

Cats 54 and 62 passed through starvation, both with and without dextrose, after removal of one adrenal. No ataxia.

Cat 60 passed through a number of starvation periods, with and without dextrose injections, after losing most of his thyroid and most of his adrenal tissue. No ataxia.

In this connection it may be added that starvation has been inflicted upon dogs, after partial removal of the pancreas, diabetic and non-diabetic, and there has been no ataxia.

Summary.

Cat 15 was male. The other ataxic cats were all female. Nothing further is known concerning the influence of sex.

Cat 19 was three-fourths grown. The other positive cases were adult. Nothing further is known of the influence of age.

The ataxic condition depends largely upon some unknown individual peculiarity. The majority of cats fail to show ataxia. A basis for this idiosyncrasy in the state of nutrition or other visible peculiarities of individual cats was not discovered.

The symptoms of the ataxia are not fully identical in all cases. Especially, minor convulsive attacks characterize some cases and not others. Mental confusion is present in some cases, not in others. The incoördination with retained muscular strength is the feature common to all.

The onset of the ataxia is always before extreme weakness has resulted. Any animal becoming dangerously weak may as well be fed, for the case is negative.

Daily dextrose administration is either essential or favorable to the occurrence of starvation ataxia. The doses should be 3 g. per kilo or above. They may be given by mouth or subcutaneously; the latter is more convenient. Commercial glucose seems to have the same action as the pure sugar.

In Cat 58, a fairly typical attack occurred without dextrose administration. But in a previous fasting period dextrose had been used. Accidentally or otherwise, it has happened that no animal kept entirely free from dextrose has shown any sign of starvation ataxia. But many negative cases are encountered even when dextrose is given.

The influence of dextrose is confirmed to some extent by Cat 15, in which the condition not only became chronic, but the acute attacks were the most violent of all. Also, the onset of ataxia was much earlier in the first fasting period, in which the doses of dextrose were larger, than in the second period, in which the doses were smaller.

Deficiency of glycogen formation is not a factor.

Simple irritation by circulating sugar molecules seems to be ruled out by the case of Cat 58.

Repeated starvation alone does not give rise to the ataxia.

Starvation along with subcutaneous injection of saline solution, saccharose, lactose, or oil has led to no ataxia.

Starvation with oral administration of starch has caused no ataxia.

The administration of adrenalin has had no effect upon the ataxia. The removal of most of the animal's adrenal tissue has not led to ataxia.

The administration of thyroid extract, or the removal of most of the animal's thyroid tissue, has had no effect in producing ataxia.

The general conclusion under question C is that the ataxia and nervous changes observed in Cat 15 may have been partly due to individual susceptibility, but otherwise were probably due to the effects of the injected dextrose.

4. Are any of the effects specific for dextrose, or may other sugars or related substances behave similarly? The case of Dog 18, in which temporary ataxia came on after a large injection of lactose, has been mentioned. The dog had previously been treated with injections of various other sugars, and the precise effect of the lactose is uncertain.

As previously mentioned, injections of saccharose and lactose offer interesting comparisons with dextrose, because these sugars are utilized to very slight extent by the tissues. In this respect the condition of the diabetic as regards his circulating sugar is approximated. The metabolic changes resulting from the compulsory burning of the injected sugar are avoided; the sugar must continue to circulate till it can finally be eliminated by the kidneys, and there is no difficulty in keeping up a constant saturation of blood and urine with sugar-molecules, fully equal to any concentration met with in diabetes. Accordingly, the opportunity is thus given to study the effects of long-continued change in the osmotic properties of the blood, and the effects of long-continued "irritation" of the kidneys by sugar.

There is a possible question as to the effects of repeated injections of large quantities of fluid, irrespective of the sugar or other substance contained in it. Hoessli described microscopic changes (fat- and lipoid-droplets in cells) in the heart and kidneys of guinea-pigs from single large injections of physiological saline, less from Ringer solution. Wideröe treated rabbits with daily injections of physiological saline solution; the animals finally died. with flabby dilated hearts, scattered capillary hemorrhages, and parenchymatous degenerations of organs. One died after 32 days,

having received 5360 g. of solution in average doses of 167 g. Another died after 50 days, having received 11,430 g. solution in doses ranging from 120 g. to 1200 g. There were no paralyses. Sudan stains for fatty degenerations were always negative. I have injected cats with saline solutions for longer than 32 days but less than 50 days. My impression is that they can endure indefinitely such doses as killed Wideröe's rabbits. Cat 36 received saline injections (30 cc. per kilo daily) during starvation, and death was little if any hastened.

The experiments with other sugars may now be considered.

Cat 21; male; weight 3400 g.

This was a young maltese adult, in excellent condition. He was kept saturated with saccharose for three months, the injections, as a rule, being either 10 g. or 20 g. saccharose, in 10 per cent or 20 per cent solution; though sometimes as much as 40 g. daily was given. Every specimen of urine was heavy with cane-sugar. The excretion must have averaged from $2\frac{1}{2}$ to 5 g. sugar per kilo daily. This would correspond, in a human patient of 60 kilo weight, to a sugar-excretion of 150 to 300 g. daily; therefore the diabetic condition was adequately imitated.

The urine was not abundant out of proportion to the volume of the injections, and remained free from reducing sugar, albumin, acetone, diacetic acid, and bile. Polydipsia, polyphagia, and emaciation were absent. The cat was perhaps more sluggish than normal, but strength, appetite, cheerfulness, and general well-being seemed not impaired. The temperature was normal, mornings, evenings 102–103. The weight varied a little up and down during the first month; at one time there was a 200 g. increase, but at the end of the month the weight was about 200 g. less than at the outset. During the second month, on the same dietary regime (horse meat always in cage), there was a marked progressive gain, so that the weight reached 4215 g. It was fat, not œdema. During the third month the gain continued, and about the middle of the month the weight was 4370 g. Granting that the cat during the first month became accustomed to the injections, the increased weight could be accounted for by simple confinement. A few days before the fastigium of the weight was reached, the concentration of solution was changed, 50 cc. 40 per cent saccharose solution being injected daily instead of 100 cc. 20 per cent solution. Either for this or for other reasons, a change

in the condition occurred. The weight fell to 3990 g. on the day before death; as nothing was eaten on the last day, it was 3765 g. at death. Diarrhea was present during the last few days. The cat became increasingly drowsy. On the last day he was weak, apathetic, and on handling "limp as a rag." The muscles were extremely relaxed. The breathing became labored. The pulse in the middle of the day was 65, the respiration 52. Temperature toward morning was 100[4], toward evening 97[6]. Weakness and lethargy increased, and death occurred about evening. There was no true resemblance to diabetic coma.

A blood-specimen taken on the last day was thick and concentrated. The red-cells were 13,500,000. The highest leukocyte count possible was 400 per cubic millimeter; this was obtainable only by counting shapeless debris, which might be the remains of leukocytes or of clumped platelets. In the stained slides, the erythrocytes were of normal appearance, but white cells were almost absent, and the very rare ones encountered were so degenerate as to be scarcely recognizable.

Autopsy. — A normal-appearing, fat animal; splendid musculature; subcutaneous and omental fat abundant; kidneys almost buried in fat. Mesenteric lymph-nodes buried in fat and enlarged to bean-size or more. Everything otherwise normal. Weights of organs:

One lobe thyroid	140 mg.
Right adrenal	450 mg.
Liver	125 g.
Spleen	12 g.
Each kidney	25 g.
Pancreas	11 g.
Heart	15 g.
Both lungs	25 g.

The intestine was tightly contracted throughout its length, and empty except for yellowish liquid, apparently glandular secretions. Examination of the gastro-intestinal contents was absolutely negative for both reducing-sugar and cane-sugar, though the last urine was heavy with cane-sugar. Apparently, therefore, an excretion into the alimentary tract did not occur.

Cultures on various media, from the heart-blood, spleen, and liver, all remained sterile. There was never a sign of infection in the cat's history. All the conditions attributed to "sugar-intoxication" remained absent.

Cat 39; female; weight 2730 g.

This cat first received saccharose through a starvation period, September 22 to October 17; there was a daily subcutaneous injection of 3 g. per kilo in 10 per cent solution. There were no "toxic" manifestations, and the cat bore the starvation practically the same as control cats; no ataxia. The injections were continued during feeding, in dosage of about 2 g. per kilo. Beginning November 29, they were omitted for a few days, and a test showed that the subcutaneous dextrose tolerance was entirely normal. The injections were then continued in dosage of 3 g. per kilo till February 24, when they were stopped permanently. The cat was later used for tests of toxic glycosuria (with organ extracts), and reacted with sugar-excretion similar to that of other cats. It is therefore assumed that the liver contained glycogen and that the permeability of the kidneys for dextrose was not appreciably altered. The interesting question of a possible alteration of permeability for saccharose was not investigated.

Here the mellituria was much higher than in human nervous disorders, and the average excretion must have been about 2 or 3 g. per kilo daily, corresponding to 120–180 g. for a 60-kilo patient. Yet the cat showed no symptoms whatever, and at the close of the experiment weighed 3240 g.

Cat 18; female; weight 2600 g.

This cat was kept saturated with lactose (*i.e.*, every specimen of urine contained lactose) during most of the time through an experiment of 5 months. Approximately the first 3 weeks of this time was on starvation. The regular dosage during this time was 3 g. per kilo subcutaneously, in 10 per cent solution. But on October 10 an injection of 6 g. per kilo was given, and on October 15 an injection of 12 g. per kilo. There was no sign of "intoxication."

Albuminuria or other symptoms or complications of diabetes never appeared. The cat remained in excellent condition. The weight at the close of the experiment was 3170 g.

Prior to the above lactose treatment, the same cat had passed through a period of glycerin injections. Consideration of this substance is therefore in order.

Glycerin is recognized as a true glycogen-former. Pflüger [(1), p. 238] accepts with a little reservation the earlier researches leading to this conclusion. Grube (3) witnessed glycogen-forma-

tion from glycerin in experiments with direct perfusion of tortoise-livers.

Cremer found glycerin to be a source of sugar in the body. Lüthje (1) undertook to furnish evidence free from the objections which Pflüger had directed against Cremer. By feeding glycerin to a depancreatized dog, he claimed to prove in objection-free manner that the body can form sugar from glycerin.

J. Schmidt took up Cremer's suggestion that the process may be reversible (especially as glycerin is found among the products of alcoholic fermentation of sugar). That is, the body may perhaps form glycerin from sugar. Schmidt therefore fed fatty acids to maximally phloridzinized dogs. The sugar-excretion was diminished, but so also was the nitrogen-excretion. From the relations of the two, Schmidt concluded that the fatty acids acted by their protein-sparing power, not by calling forth glycerin formed from sugar to be combined with them into neutral fat. [This of course does not prove that the body does not or cannot under any conditions form glycerin from sugar.]

Knapp performed three metabolism experiments showing that glycerin spares protein and hence has nutritive value.

Reach (1*A*) studied the destruction of glycerin by organ extracts and in perfusion experiments. He concluded that the liver synthesizes a small amount of glycerin into diacetic acid.

Magnus-Levy [(4), p. 121] gives references showing that glycerin in large doses, up to 200 g., increases the excretion of uric acid.

Lepine [(1), p. 117] quotes Luchsinger (Pflügers Arch. XI, 1875) as having proved that glycerin completely prevents glycosuria after piqûre. Richter's explanation is also given, that glycerin inhibits the formation of sugar from glycogen. According to Luchsinger's experiments, post-morten glycogenolysis is likewise retarded in the livers of animals which received glycerin injections before death.

Ransom in 1887 carried on the study further, and found that glycerin given by mouth prevents or markedly diminishes the glycosuria due to morphine, amyl nitrite, and piqûre. Glycerin is less effective in this respect when given subcutaneously. He concluded, like Richter, that its effect is upon the liver, and is to inhibit the transformation of glycogen into sugar. The plausibility of this opinion is somewhat increased by the knowledge that a drug such as arsenic, for example, has an effect in inhibiting glycosuria after piqûre, or sugar-formation during perfusion.

Hermann reported increased ferment-content of the urine after glycerin feeding.

Starkenstein (1), studying the liver-diastase, called attention to the fact that glycerin is an excellent solvent of ferments. After glycerin-feeding in rabbits he found the diastase of the liver decreased (2 experiments) and that of the urine increased (1 experiment). He therefore concluded that the effect of glycerin is to wash out the diastase from the liver, and thus diminish glycogen break-down. He found adrenalin glycosuria not prevented by glycerin feeding, and considered therefore that other factors than ferments must here be concerned. The opinion that other factors than ferments are concerned is the most valid of Starkenstein's assumptions. The results of diastase-determinations are unreliable to decide such questions. The idea that glycerin prevents glycogen-destruction in the living body by dissolving diastase out of the liver may be rejected on the ground of essential improbability.

Munk (2) injected glycerin intravenously. The doses were a little over one gram per kilo, and the injections were given very slowly. He found that glycerin under these conditions burns, and spares fat.

Vetleson reported a case of pernicious anemia improved by glycerin. It has, however, not won a place in the therapy.

Williams' textbook of obstetrics describes the use of 100 cc. sterile glycerin as an intra-uterine injection to induce labor, but cites authors who found the practice dangerous. Glycerin-poisoning under these conditions is said to be characterized by hemoglobinuria, albuminuria, fever, cyanosis, and occasionally death.

Schmey reported a rare case of glycerin habit, a youth who consumed incredible quantities of glycerin for a long period. The alcohol-nature of glycerin appears from Schmey's description to have been manifested here. The drug seems to have been taken for the sake of some pleasant effect, either exhilarating or sedative, which was felt from it. The principal consequences were the usual physical, mental, and moral deterioration which attend most drug-habits.

The glycosuria of diabetes is not checked by glycerin. Also as a food for diabetics, glycerin has proved of little or no value. Though it may be well borne at first, later it generally increases the glycosuria.

There seems to have been no investigation dealing with the long-continued administration of glycerin, in doses insufficient for acute symptoms, with a view to observing any possible chronic or metabolic effects. In fact, with the exception of a few poisons, like lead and arsenic, the entire field of chronic intoxications has been very slightly touched in laboratory research. Investigators have contented themselves with the easier observation of acute symptoms. The formation of glycogen and of sugar from glycerin, and the inhibition of glycosurias by the supposed action of glycerin upon the liver, give cause for drawing glycerin within the scope of any thorough study of diabetes and glycosuria.

Cat 18 received subcutaneous injections of glycerin for a little over two months. Glycerin injections are locally more irritating than sugar, and 5 per cent was the strongest solution considered advisable. The dose was generally 50 cc. of this solution, or about 1 g. pure glycerin per kilo of normal weight. An initial loss of weight was due to an unsuitable cage. In a healthful cage, the cat gained weight during glycerin treatment, and showed no abnormal behavior. The urine remained free from sugar, acetone, diacetic acid, bile, and albumin. No other tests were made.

Larger doses or a longer time might have brought some positive result. It seemed advisable, however, to drop this experiment; and, accordingly, after a period of rest, the cat was used for lactose injections as already described. Later, this cat which had passed through periods both of glycerin and of lactose injections, was used in experiments concerning toxic glycosuria and emotional glycosuria, and reacted like a normal cat. Also, in an experiment beginning April 18, the dextrose-tolerance was found entirely normal.

The general conclusion respecting question 4 is that the effects observed in Cat 15 are specific for dextrose, so far as the control experiments with cats can decide. It must be recognized, however, that all the control experiments were for a much shorter period than the experiment with Cat 15, and that incoördination was observed in Dog 18 after a large lactose injection.

It seems reasonable that the effects concerning liver-glycogen might be specific for dextrose. The possible effects of long-continued levulose injections might be very interesting for comparison, as also the question whether an animal like Cat 15 can form glycogen from levulose. It would not be surprising if the effects upon the nervous system should be specific for dextrose

or other assimilable sugars. It would only mean that the nerve-cells (or perhaps other cells) respond to the chemical stimulus of the sugar-molecules which they must burn, but not to the physical stimulus of sugar-molecules which they cannot utilize.

Possible specific differences respecting the sugar-tolerance might be most interesting of all. If long-continued injection of one sugar renders the kidney less permeable only for that one sugar, the fact would be of decided interest. Distinctions of this sort might conceivably be found even between dextrose and levulose. Injections of saccharose and lactose have apparently not altered the permeability for dextrose.

General Conclusions.

The presence of long-continued excess of assimilable or non-assimilable sugar in the normal organism does not produce diabetes nor any of the symptoms or complications of diabetes which have been attributed to hyperglycemia. As far as the experiments with normal animals can decide, sugar-excess alone cannot give rise to diabetes, but some other cause must first be present before sugar can manifest its injurious effects in weakening the assimilative power. In this respect the experiments agree well with the best clinical observations; but a continuance of the inquiry (Chapter XIII) will be necessary before the evidence from the experimental side is complete.

Other effects of prolonged sugar-injections seem to offer points of unique interest, but the observations are too few to permit positive conclusions.

CHAPTER IV.

PARENTERAL FEEDING.

PARENTERAL alimentation, or the giving of food by ways other than the alimentary canal, is not seriously considered in present-day medicine. A few physicians have entertained considerable hopes of the method; a smaller number have claimed favorable results from its use; but in the experience of most who have tried it, it has proved either useless or harmful. In contemporary practice, patients unable for any reason to eat the necessary quantity of food receive some doubtful help from nutrient enemas; otherwise they starve. And yet, a thorough investigation of the parenteral method has never been made.

The earliest attempts, before the time of asepsis, involved the injection of considerable quantities of milk or other ordinary foods under the skin. The method received its first scientific impetus when it was taken up by Leube, Voit, and other earlier workers, with suitable methods and precautions. These earlier investigators took it for granted that assimilation meant benefit. Accordingly, their only interest was to prove which foods could be thus introduced, and how many calories could be supplied to the body by this means.

The literature of the subject may be reviewed under the three headings of protein, fat, and carbohydrate injections.

1. Protein Injections.

Protein injections may be dismissed very briefly. They were early found to be useless and also harmful. A few quotations will suffice.

Mariani in 1897 attempted subcutaneous alimentation in rabbits with various substances. The protein used was the yolk and white of egg. He found that the injections were harmful, and injured the kidneys.

Corradi in 1898, also Barbèra in 1902, tried somatose as a protein for subcutaneous use. Both of them concluded that subcutaneous injection of any sort of foodstuff was of little if any value.

Credé in 1904 published a thorough investigation and full literature.

Schmidt and Meyer in 1906 tried the intraperitoneal injection of certain special albuminous preparations, but their results are not encouraging.

Heilner (6) administered to rabbits about one eighth the animals' own weight of horse-serum, either by mouth or subcutaneously. His observations concerning the elimination of water and nitrogen are interesting, but the work was not intended as a basis for parenteral feeding with serum.

2. Fat Injections.

Leube (1) rejected albumin injections as injurious. He also rejected sugar solutions, because the strong ones are painful and may even cause sloughing, while with weak solutions not enough calories can be introduced. He considered fat the ideal food for subcutaneous use, because it can be given in large quantities, has the highest caloric value, and is entirely non-irritating. Leube published experiments tending to show that large injections of sterile butter may be borne well by dogs, and apparently be slowly absorbed and utilized.

Mariani tried oil, among other foods, in rabbits, and assigned to it the highest rank of all, claiming that the subcutaneous injection of oil reduces nitrogen-excretion to a minimum and in some cases prolongs life. Conclusions like these, which are the opposite to the truth of the case, prove chiefly that the rabbit is an uncertain animal.

Corradi in 1898 concluded that oil injected subcutaneously in human patients produces no ill effects, and is quickly absorbed and utilized.

Jacob at the Congress in 1898 expressed the belief that human patients can absorb several hundred cubic centimeters of subcutaneously injected oil within a day or two. But on this point he was corrected by Müller (1).

Perrier injected 10 cc. olive oil beneath the skin of fasting rabbits, and noted that they died as soon as the controls, and that most of the oil was still present under the skin at autopsy. But he claimed that the injected rabbits excreted less nitrogen than the controls.

Barbèra used injections of olive oil, among other substances, and found that the subcutaneous doses are very slowly absorbed

in the dog. This was found to be the case likewise with emulsified oil, and even with the fat-bearing lymph of another dog.

Winternitz used subcutaneous injections of oil in human patients, mostly in cases of carcinomatous obstruction of the bowel. His conclusion was that subcutaneously injected fat may in time be completely absorbed and utilized, but absorption is so very slow that the treatment is useless. After injection of 500 g., only 2 or 3 g. per day is absorbed, and months would therefore be required to absorb the whole.

Henderson and Crofutt investigated the question in accurate fashion, using cottonseed oil. They came to the conclusion that oil injected subcutaneously is readily and widely diffused through the subcutaneous spaces. Such oil is not, however, transformed *in situ* into adipose tissue. It acts as a non-irritating foreign substance. It does not appear in detectable amounts in blood, lymph, or milk. It is ultimately absorbed and used in metabolism, but the process is one of extreme slowness. Their experiments overthrow Leube's ideas concerning the utilization and benefit of injections such as his large doses of butter in dogs.

Schmidt and Meyer tried injection of olive oil and of iodipin intraperitoneally. The injections were well borne by human patients, but even in the peritoneum, absorption and utilization of the oil were found to be very slow.

Heilner (5), by careful metabolic (including respiration) experiments, proved that oil given by mouth does not spare albumin in starving animals, and given subcutaneously it markedly increases the excretion of nitrogen. He agrees with former writers that the oil is absorbed very slowly from the subcutis.

3. Sugar Injections.

A. Pioneer Work with Sugar.

As already noted, Leube had bad results, including even necrosis of the skin, from subcutaneous injection of concentrated sugar solutions, and he therefore concluded that not enough calories can be introduced in the form of sugar to make the attempt worth while.

Fritz Voit (1 and 2) used 10 per cent solutions, and found that several hundred cubic centimeters could be introduced under the skin of the thigh without special discomfort to the patient. The sugar thus injected did not appear in the urine, and its utilization

and consequent benefit were taken for granted. The quantity thus administered represented a considerable fraction of the total daily caloric requirements of the patient, and calories were the principal interest of Voit and his contemporaries.

Müller (1 and 2) found subcutaneous injection of 10 per cent dextrose solution painful in himself. But the description of the effect indicates a slight infection. Chemical irritation would be less likely to wait twelve hours before beginning to manifest itself.

Lilienfeld attempted experiments with intravenous nutrition in rabbits. He injected dextrose and levulose solutions, and found the former preferable. The injections were of 2.85 g. to 15 g., in 3 to 5 per cent solution, given very slowly. He did not analyze either for glycogen formed or for nitrogen excreted, and the only thing demonstrated was that most of the injected sugar was retained. The author concluded that his results were encouraging. As a matter of fact they were not encouraging. The rabbits frequently showed albuminuria, enteritis, weakness, and even death. Lilienfeld's claim that sugar is utilized better and is less harmful if given in alkaline solution (0.2 per cent soda) is interesting if found true.

Corradi and also Barbèra included sugar among the list of substances which they injected, and concluded that no kind of subcutaneous alimentation is of any real value.

Schmidt and Meyer injected, among other substances, dextrose, maltose, and dextrin into the human peritoneum. Their work is of interest chiefly as showing the tolerance and the by-effects; it permits no conclusions whether the substances were of benefit as foods. A solution of 5 per cent dextrose was painless when injected into the peritoneum of a human patient, but the autopsy showed pronounced irritation of the peritoneal surfaces. The authors say that 10 per cent solutions are painful in human patients, and suggest that human tissues are more easily irritated than those of animals.

B. Glycogen-Formation from Sugar Injections.

C. Voit published a series of researches performed in his laboratory concerning glycogen-formation. That of Lusk in particular proved that glycogen is formed from sugar given subcutaneously.

Gumprecht reported that subcutaneous sugar-injections may produce as much as 3.9 per cent glycogen in the liver. This is as

good as the results from intrastomachal injections of cane-sugar n starving rabbits by Külz (2). After doses of 21 g. saccharose, Külz found in the livers only 2, 3, or 4 g. glycogen.

Since we have seen in a former chapter how the body strives to maintain its glycogen-supply, sacrificing even protein for the purpose, it may be set down as one point in favor of dextrose injections, that they at least aid in this important task in the starving organism. Even if the injections cause the breaking down of a little protein, they may possibly more than repay the loss by the glycogen which they contribute.

C. Nitrogen-Excretion After Sugar Injections.

Mariani claimed that small doses of sugar subcutaneously diminish the nitrogen excretion and the loss of weight in fasting rabbits.

Kossa demonstrated increased nitrogen excretion after subcutaneous injection of $2\frac{1}{2}$ to 7 g. saccharose per kilo in dogs and rabbits. Certain writers [Magnus-Levy (4), p. 161; Pflüger (1), p. 451] convey an impression as though Kossa's proof extended to sugars in general.

Nobecourt and Bigart showed that injections of dextrose into the peritoneum of rabbits, in doses sufficient or insufficient for glycosuria, caused increase of the urea excretion. Large doses caused increased excretion of chlorides.

J. Scott, using dogs, was apparently the first person to prove that large injections of dextrose, 5 to 7 g. per kilo, cause a well-marked increase in the excretion of total nitrogen. He thought that the nitrogen-distribution was altered, a larger proportion being in the form of ammonia and less in the form of urea; and he also wrongly considered that dextrose acts as a protoplasmic poison, like phosphorus.

Underhill and Closson (3) repeated the work of Scott, injecting 5 to 7 g. dextrose per kilo subcutaneously in dogs. They found the total nitrogen increased as a result of the injections, and the relative percentages of different nitrogenous constituents unchanged. They were the first investigators to demonstrate correctly the effects of large subcutaneous injections of dextrose upon the nitrogen excretion.

Heilner (1 and 3) has published important researches on this subject, working with rabbits. His results are specially complete because he followed not only the nitrogenous metabolism but also

the respiratory quotient. His fasting rabbits received on the third or fourth day of fast about 31 g. dextrose (about 10 g. per kilo) by mouth or subcutaneously, in 10 per cent solution. In each case, he found a decrease of the nitrogen-excretion, and also a diminution of the total metabolism. The latter was ascribed by him to neither the sugar nor the accompanying water as such, but to a disturbance of osmotic relations in the body. In the second paper on this subject (3), he concludes that a large injection of a solution, foreign in composition to the tissue fluids, produces diminution of the power to burn albumin, while the power to burn fat is unimpaired. Heilner (6) obtained results which again prove that the rabbit is an exceptional animal. By injections of 300 cc. of 10 per cent saccharose solution subcutaneously in rabbits (about 10 g. per kilo), he found that protein metabolism is markedly diminished, especially on the day of injection. Fat metabolism, on the contrary, is markedly increased. These results are not due to any sparing action of the sugar, but are concluded by Heilner to be due to an osmotic injury to the organism. Injections of strongly hypertonic salt or sugar solution often result in diminution of urine. [All these results would have been impossible in animals which better reproduce human conditions.] Heilner (4) proved that urea injections cause a pronounced increase of nitrogen excretion, over and above that represented in the urea itself.

The excessive sensitiveness of rabbits to disturbance of any sort is well illustrated by the finding of Freund and Grafe, that even the introduction of a stomach-tube, by "shock," can reduce the oxidation-processes of this animal by 10 to 20 per cent.

D. Claims of Benefit Resulting from Sugar Injections.

The most complete work on this subject is that of Fichtenmayer in Leube's laboratory in 1908. Fasting rabbits were used. The following tables as arranged by Fichtenmayer show the results obtained. For the sake of completeness, Fichtenmayer's glycogen experiments are here included.

EXPERIMENT II (Control)

Day	Weight of Animal	Quantity of Urine	Spec. Grav. of Urine	Nitrogen	Substance injected	Sugar	Albu
I	2510	60	1055	0.61	---	---	---
2	2440	60	1050	0.64	---	---	---
3	2395	70	1030	0.50	---	---	---
4	2345	50	1030	0.42	---	---	---
5	2295	50	1030	0.42	---	---	---
6	2260	100	1029	1.07	---	---	---
7	2230	100	1020	1.01	---	---	---
8	2147	100	1020	1.52	---	Neg.	Trace
9	2055	150	1032	2.06	---	Neg.	Trace
10	2000	210	1032	1.84	---	Neg.	Trace

EXPERIMENT IV (By Mouth)

1	2230	250	1020	1.07	---	Neg.	Neg.
2	2175	130	1030	0.92	---	---	Neg.
3	2095	230	1010	1.49	---	Neg.	Neg.
4	2010	250	1010	2.17	20g.dextrose and 100cc.phys.saline sol.	Neg.	Neg.
5	1925	300	1020	2.09	ditto	---	---
6	1890	260	1025	1.97	ditto	Neg.	Neg.
7	1790	250	1019	2.60	25g.dextrose and 106cc.phys.saline sol		Trace
8	1790	270	1015	1.67	100cc. saline sol.	Pos.	Trace
9	1690	250	1021	1.88	ditto	Pos.	Trace
10	1630	150	1021	1.82	ditto	Pos.	Trace
11	1495	260	1015	2.28	ditto	Pos.	Trace
12	1460	210	1018	2.14	---	Pos.	Trace
13	1430	300	1010	3.66	Death	Neg.	Neg.

EXPERIMENT VI (By Mouth)

1	1860	200	1014	0.81	---	Neg.	Neg.
2	1805	160	1020	0.84	---	Neg.	Neg.
3	1745	180	1015	1.29	---	Neg.	Neg.
4	1630	250	1014	1.50	15g.dextrose and 100cc.phys.saline sol.	Neg.	Neg.
5	1480	250	1030	1.93	ditto	Neg.	Neg.
6	1405	210	1017	2.15	ditto	Neg.	Neg.
7	1350	360	1012	2.94	20g.dextrose and 100cc.phys.saline sol.	Neg.	Trace
8	1295	260	1014	1.80	22g.dextrose and 100cc.phys.saline sol.	Neg.	Neg.
9	1280	500	1010	1.04	100cc.phys.saline sol. without sugar	Pos. (slight)	Neg.
10	1165	250	1010	1.04	Death	Neg.	Trace

EXPERIMENT VIII (By Mouth)

1	2270	150	1010	0.85	---	Neg.	Neg.
2	2230	130	1010	1.06	---	"	"
3	2100	160	1020	1.59	---	"	"
4	1900	240	1022	3.26	15g.dextrose and 100cc.phys.saline sol.	"	"
5	1800	180	1020	1.79	---		
6	1700	140	1020	2.30	---		Trace
7	1585	260	1022	3.66	20g.dextrose and 100cc.phys.saline sol.	"	Neg.
8	1500	150	1022	2.12	---	"	"
9	1385	210	1022	2.88	Experiment interrupted	"	"

EXPERIMENT IX (Subcutaneously)

1	1745	220	1015	0.55	---	Neg.	Neg.
2	1670	220	1016	1.20	---	"	"
3	1620	140	1012	1.12	---	"	"
4	1505	170	1020	1.84	25g.dextrose and 30cc.phys.saline sol.	"	"
5	1480	170	1024	1.74	50g.dextrose and 60cc.phys.saline sol.	"	"
6	1490	170	1029	*6.77	---	2.2%	Trace
7	1400	150	1018	0.58	30g.dextrose and 100cc.phys.saline sol.	Neg.	Trace
8	1340	130	1015	1.09	50g.dextrose and 100cc.phys.saline sol.	"	Pos.
9	1320	140	1015	0.84	30g.dextrose and 100cc.phys.saline sol.	1.8%	Neg.
10	1375	190	1034	0.98	15g.dextrose and 30cc.phys.saline sol.	1.%	Pos.
11	1275	150	1012	1.29	Death	0.7%	Neg.

*Possibly a misprint for 0.777

EXPERIMENT X (Subcutaneously).

Day	Weight of Animal	Quantity of Urine	Spec.Grav. of Urine	Nitrogen	Substance injected	Sugar	Albu.
1	1620	290	1016	0.24	---	---	---
2	1500	220	1006	0.52	---	---	---
3	1480	140	1015	0.72	---	---	---
4	1415	170	1015	1.27	30g.dextrose and 50cc.phys.saline sol.		
5	1400	160	1016	0.73	30g.dextrose and 80cc.phys.saline sol.	6.2%	Neg.
6	1400	250	1014	0.31	30g.dextrose and 100cc.phys.saline sol.	Neg.	"
7	1410	200	1008	0.42	---	"	"
8	1330	250	1008	2.14	30g.dextrose and 100cc.phys.saline sol.	"	"
9	1290	240	1010	1.18	30g.dextrose and 100cc.phys.saline sol.	"	"
10	1335	240	1010	0.78	30g.dextrose and 100cc.phys.saline sol.	"	"
11	1340	200	1012	0.49	30g.dextrose and 100cc.phys.saline sol.	0.8%	Trace
12	1210	180	1011	0.65	---	Neg.	Neg.
13	1170	160	1020	1.23	Death.	"	"

EXPERIMENT XII (Glycogen--Subcutaneously).

1	1580	320	1010	1.05	---	---	---
2	1490	150	1012	1.16	---	---	---
3	1430	180	1010	1.38	---	---	---
4	1300	160	1022	1.80	---	---	---
5	1190	250	1005	1.81	40g.glycogen and 50cc.phys.saline sol.	Neg.	Trace
6	1090	220	1012	1.96	Death.	"	Pos.

EXPERIMENT XIII (Glycogen--Subcutaneously).

1	2100	300	1020	0.84	---	---	---
2	2000	280	1016	0.95	---	---	---
3	1800	260	1010	1.61	10g.glycogen and 50cc.phys.saline sol.	---	---
4	1700	260	1010	1.45	5g.glycogen and 25cc.phys.saline sol.	---	---
5	1630	300	1020	1.47	10g.glycogen and 50cc.phys.saline sol.	---	---
6	1560	416	1003	1.40	5g.glycogen and 25cc.phys.saline sol.	---	---
7	1430	296	1015	1.66	10g.glycogen and 100cc.phys.saline sol.	---	---
8	1380	306	1022	2.46	10g.glycogen and 50cc.phys.saline sol.	Pos.	Trace
9	1305	280	1018	1.56	Death.	0.4%	Trace

EXPERIMENT XIV (Glycogen--Subcutaneously).

1	2016	200	1005	0.53	---	---	---
2	1970	270	1005	1.20	---	---	---
3	1950	310	1005	0.93	---	---	---
4	1920	280	1005	1.13	20g.glycogen and 60cc.phys.saline sol.	---	---
5	1910	310	1010	1.19	10g.glycogen and 50cc.phys.saline sol.	0.3%	Trace
6	1910	300	1004	1.05	Death.	1.8%	Trace

A translation of Fichtenmayer's own conclusions from his experiments is as follows.

"1. In opposition to the results of other authors, I have found that neither inflammatory reactions nor gangrene of the skin occurred, though I often injected concentrated sugar-solution.

"2. The animal tolerates the concentrated solutions thus injected for a considerable time without reacting by glycosuria.

"3. As my tables plainly show, sugar is an albumin-sparing substance also when injected subcutaneously. I have invariably obtained positive results with the subcutaneous sugar-injections. Especially in the last two experiments [IX and X] I succeeded in preventing any increased albumin breakdown, clear up to the death of the animal. Only in regard to an increased duration of life have I, as opposed to other investigators, obtained no favorable results. But I believe that I may explain this result by the fact that my animals were all fresh from the country, that is, were more poorly nourished than those in the Clinic.

"Concerning glycogen I cannot venture a definite opinion. It is certain that glycogen subcutaneously injected is used in the metabolism and is only to a small extent excreted in the urine as sugar. On the other hand, a direct sparing of albumin could not be demonstrated, even though the nitrogen excretion of the fasting animal after injection of glycogen increased less markedly than in the control animal. But in no event is glycogen to be placed on a par with sugar as an albumin-sparing substance. Inasmuch also as the animals died within a short period after the glycogen injection, I could not escape the impression that glycogen often exerts a direct toxic effect."

It may be noted in passing that not improbably there were dextrins in the urine of Fichtenmayer's glycogen-injected rabbits, which his analyses for sugar and glycogen failed to detect. But the most notable points in the research are the high sugar-tolerance of the rabbits, and the diminished nitrogen excretion in consequence of huge subcutaneous injections of dextrose. Fichtenmayer's work is an interesting and valuable determination of conditions in the rabbit. It has no application to any other species of animal, and especially not to man. This restriction is the penalty paid by anyone who performs this class of experiments upon the most erratic and unreliable of known animals. Warning should have been taken from the discovery of Heilner, that large sugar-injections cause in rabbits an osmotic injury which not only markedly reduces the nitrogen-output on the day of injection, but also diminishes the animal's entire metabolic activity. In more reliable species, it would be impossible to give such huge sugar injections, or even half the dosage, without witnessing a very marked increase of the excretion of nitrogen. The rabbits were not benefited by the injections, as is proved by the failure to prolong life. They were exceptionally strong rabbits, to have borne such sugar injections at all; and a sufficient number of controls would probably have shown that the injections shortened life.

Laguesse [(7), p. 349] reports that a snake weakened from prolonged starvation became active and lively after a subcutaneous injection of dextrose.

Marrassini (1) fed his normal rabbits with 100–150 g. cabbage. But when certain animals (for a study of the pancreas) received daily subcutaneous injections of 15–20 g. dextrose per kilo, they were able to hold weight and thrive on 30–35 g. cabbage per day. As noted heretofore, rabbits receiving large sugar-injections do tend to eat less than normal, but they do not hold weight. Either œdema or some other accident was responsible for Marrassini's findings, for the result as stated is impossible.

The most recent work with parenteral nutrition is that of Ornstein, with mixed injections. He concluded that dogs burn completely a mixture of foreign blood-serum and dextrose solution, subcutaneously injected, for a period of 8–12 days, and utilize it well; but the value is less than by enteral administration. If prolonged beyond this period, the treatment causes increased protein destruction, emaciation, and finally death with anaphylactic symptoms. A mixture of serum, dextrose, and emulsified olive oil is not suitable for subcutaneous nutrition; it causes a prompt increase of protein destruction, and after a short time death. [Notwithstanding these interesting findings, it may still be questioned whether injections of foreign prŏtein are ever really beneficial, and whether the life of a starving animal could be prolonged thereby.]

The only other reports claiming benefit from sugar-injections are those recently published by Kausch and his assistant Berendes.

Kausch states that he has tried injection of other food-substances, but nothing is equal to dextrose. He asserts that subcutaneous injection of 5 per cent dextrose solution hurts nobody; stronger solutions are painful. The sugar is dissolved in physiological salt solution. His intravenous injections are of 5 per cent to 10 per cent concentration, and in necessary cases a little adrenalin is added. The doses are up to a litre, and once two litres was given intravenously. There has never been a sign of any ill effect. The intravenous route is more agreeable than the subcutaneous for both patient and operator. He now uses the subcutaneous method only for small children or other patients for whom the intravenous method is unsuitable. Kausch recites the case of a woman with puerperal sepsis, with daily fever above 40 degrees. She received as high as 2900 cc. of sugar-solution daily for six days, and excreted only the trifle of 0.2 g. to 3 g. Another patient was a man with a carcinoma of the papilla of Vater and an open biliary fistula. He received 10 intravenous infusions in

11 days, representing a total of 958 g. dextrose. Kausch considers that the dextrose infusions can be credited with saving the lives of both these patients. He claims that the patients who are worst off show the best effects; and that the results from dextrose in desperate cases are both more noticeable and also more lasting than from saline and adrenalin infusions. Kausch "assumes that the sugar is burned." Metabolism experiments are promised later. Meanwhile, he strongly urges the use of dextrose infusions not only in serious surgical cases, but also in medical conditions in which the body stands in need of either food or water, for example, gastro-intestinal troubles, hysterical and gravid vomiting, and above all for cholera, in which the intravenous dextrose solutions should supply both food and water to the tissues impoverished of both.

The statements of Berendes are to similar effect. If a patient receives physiological saline subcutaneously on one side of the body, and 5 per cent dextrose solution on the other, he cannot distinguish between them. As much as 750 cc. of 10 per cent dextrose solution has been given intravenously without any glycosuria. A litre of the 10 per cent solution intravenously caused only a trace of glycosuria. No harm ever resulted.

Magnus-Levy [(4), p. 161] mentions Forster's observation of increase of urea from 12.5 g. to 17.9 g. in a fasting dog after intravenous injection of 300 cc. of 25 per cent sugar solution. The effects of large intravenous injections of this sort will be treated in the chapter on diuresis; they do not belong here.

4. What Can be Expected from Parenteral Alimentation.

One of the simplest dictates of common sense with regard to this subject ought to be, that we cannot expect a food, especially sugar, to be any better borne or to yield any better results when given parenterally than when given by the usual digestive route. Simple as this truth is, it has never been applied in the study of this subject. Why do the textbooks state that sugar given subcutaneously increases instead of diminishing the excretion of nitrogen? Because the large doses given subcutaneously by workers like Scott, or Underhill and Closson, resulted in an increased excretion of nitrogen. But it is forgotten that these investigators were studying chiefly diabetes and the toxic properties of sugar. Large doses were proper in their work. But when we turn to the subject of subcutaneous nutrition, it will be seen

that their doses, namely, 5 to 7 g. per kilo, applied to a 60-kilo human being, mean a dosage of 300 to 420 g. dextrose. Nobody would ever recommend such quantities to be taken at one time as part of a patient's regular diet. Their harmful effects, and the acute sickness which they would cause in a large proportion of human beings when taken by mouth, are perfectly well known. Therefore, from the nutritional standpoint, work like that of Scott and Underhill means essentially that doses of sugar which are harmful when taken by mouth are also harmful when injected subcutaneously.

Large carbohydrate meals are not taken in the form of sugar, but in the non-irritating form of starch. The osmotic and irritant properties of sugar must be borne in mind in giving it either enterally or parenterally. And as the physician generally makes his subcutaneous dose about half the dose by mouth, and his intravenous dose perhaps smaller still, some similar rule will probably be found to apply in the use of dextrose. Here the original objection of Leube may be raised, that in this way not enough calories can be given to make the attempt worth while. That may be true. But at any rate, this is one of the limitations of the method, and should not be lost sight of.

But, supposing that suitable doses of sugar parenterally may be as beneficial as similar doses by mouth, what is to be expected of them? In this discussion, for the sake of completeness, we shall include also oil and other non-nitrogenous, non-carbohydrate food-substances. So the broad question is, since protein substances cannot profitably be given parenterally, what is the utmost to be hoped from other food-substances, even granting that the benefit from them when given by this method may be as great as the benefit from them when given by mouth?

There are three classes of animals to which such food-substances may be administered, viz., full-fed animals, insufficiently fed animals, and fasting animals. For the first two classes, the facts are well understood. Non-nitrogenous food-substances when given (by mouth at any rate) to full-fed animals may give rise to deposit of fat; when given to insufficiently fed animals they may yield energy, spare protein, and fill out the insufficient diet so that it may become sufficient. But in fasting animals, conditions are somewhat different. Though the feeding of non-nitrogenous energy-bearers may sometimes spare nitrogen in brief experiments, the general evidence indicates that when given through longer

periods of fasting, they do not save nitrogen and do not prolong life.

Mention has already been made of the experiments of Heilner (5), proving that oil given by mouth does not spare albumin in a fasting animal, and given subcutaneously markedly increases the excretion of nitrogen.

Kaufmann fed one series of fasting rabbits on oil, and another series on cane-sugar. The fed animals died in shorter time than the controls, and, in general, nitrogen was not spared. The oil-fed animals in particular died within 3 or 4 days, after having shown increased nitrogenous excretion from the outset. Two of the cane-sugar rabbits lived an unusually long time, but it is possible that they were exceptions. Kaufmann himself interpreted his work in a somewhat different manner, but the facts are as stated, and are in line with the later researches in this subject.

Falta and Gigon (2) published work in accord with the previous researches of Voit and Korkunoff (Ztschr. f. Biol., 32, 1895). Their conclusions are, that with the duration of previous hunger, the rapidity of albuminous katabolism increases, while the protein-sparing power of carbohydrate fed with protein decreases. Inosit and alcohol (non-glycogen formers) are not thus affected by hunger.

Pari found that feeding of B-oxybutyric acid diminishes albumin destruction. Carbohydrate (in this case cane-sugar) after long hunger loses its power of diminishing protein katabolism, while non-carbohydrate sources of energy (fat, β-oxybutyric acid) do not thus lose their slowing effect.

Wimmer came to the following conclusions. (1) The protein-sparing power of starch increases at a diminishing rate with increased administration, to a maximum of about 55 per cent. (2) The sparing power of starch and of glucose is approximately equal. (3) The maximum sparing power of starch exceeds that of gelatin. (4) Sparing power may be influenced by pathological conditions (in this case a sarcoma).

Reference may also be made again to the case mentioned by Kossa (1), of serious disturbance of health, supposedly leading indirectly to death, in an investigator who subjected himself for a limited time to a diet of nothing but sugar.

Special attention should be given to the series of researches by Schulz and his pupils. The dissertation by Augustin is a part of this work. These publications are as long as they are interest-

ing, and can be barely touched here. In these experiments, sugar seemed to be able to spare nitrogen at all stages of starvation, but did not seem to add strength after the dog was very far gone. A dog was starved to this point: "The animal had to be lifted out of his cage and carried. Control of the hind legs was entirely lost; they hung as if paralyzed. With the front legs the animal made unsuccessful attempts to raise himself. The eye was as if broken. The heart-action was very irregular. In a word, the dog seemed dying." Milk was given cautiously by tube, and retained. On the three succeeding days, meat was fed. The diet on each of the four days was *insufficient*, yet the animal rapidly gained strength, and could be starved *several weeks* longer. Schulz's opinion is that the final weakness of starvation is not a mere exhaustion of food-materials, but a kind of auto-intoxication.

Augustin's dissertation recites that another dog was about to die of extreme weakness on the 30th day of starvation, having lost appetite as well as strength. Then for eight days he was fed with *insufficient diet;* then starved for four days; then fed again for seven days on *insufficient diet*, the nitrogen excretion being constantly greater than the intake. The dog gained strength and well-being from the feedings. At the very end there was a rapid decline, and death occurred on the 50th day.

All these quotations may be discussed in review as follows.

A. There is some interest in Wimmer's observation that the sparing power is modified by pathological conditions (in accord with the general notions of "toxic" destruction of protein in such conditions). For such conditions are the very ones in which sugar is most likely to be used clinically.

B. Schulz's experiments clearly overthrow the popular impression regarding death from starvation. Schulz's conclusion of an "auto-intoxication" does not necessarily hold, and it is better not to import that much-abused term into this subject. An animal dying of starvation does not by its symptoms suggest an intoxication. It suggests rather an engine which is stopping for want of fuel. The case can be explained in simple terms by supposing that a starving animal dies, exactly according to the popular impression, because it has used up all of its body-reserve that is available. The insufficient food that is given either supplies certain substances which the body can no longer supply, or in some unknown manner it renders available that portion of the

reserve which otherwise was not available, so that the animal can continue for some time longer to live from its own tissues.

C. There is some disagreement, as, for example, between Pari and Heilner concerning the sparing power of fat, and between Pari and Schulz concerning the sparing power of sugar at late stages. Whatever the results of brief experiments, they do not alter the fact that animals fed daily on either fat or sugar may die sooner than animals on plain starvation. The reason is unknown. It may perhaps be an increased wear and tear of cell-constituents which cannot be replaced by non-nitrogenous food. Further study seems desirable.

5. Special Disadvantages in the Parenteral Introduction of Sugar.

The above limitations apply when sugar is given by the natural intestinal channel. But the parenteral method involves certain special disadvantages in addition. These arise from the water which must be injected along with the sugar, and also from the crystalloid, osmotic properties of the sugar itself.

Sugar cannot conveniently be used in human patients except in very weak solution, certainly no stronger than 10 per cent. A large quantity of water thus accompanies every dose of sugar. For this reason a certain amount of nitrogen-loss is inevitable in any fasting animal. Even the drinking of a large quantity of water, though without effect in a well-fed organism, during fasting results in an increased excretion of nitrogen. The majority consider this effect due to a simple "washing out" of extractive nitrogen, but others hold that the surplus supply of water causes an actual increase of metabolism [see references by Hammarsten, p. 862]. Large injections, even of plain saline, are followed by increased nitrogen loss in fasting animals. Among those who have studied the question is Trosianz. In his experiments, no special increase of nitrogen excretion was observed from hypo- or isotonic NaCl solution injected subcutaneously during nitrogenous equilibrium with food rich in NaCl; and only a little increase after injection of hypertonic solution. But in hunger, both NaCl and urea solutions caused a marked increase of nitrogen elimination.

Sugar solutions, as a rule, cause a somewhat greater increase of nitrogen excretion than corresponding salt solutions. An increased nitrogen-loss apparently attends the parenteral introduction of any considerable amount of any crystalloid substance. Parenteral feeding would logically be most used in patients who

eat little or nothing, and these are the ones in whom it most easily produces nitrogen loss. Special disadvantages in regard to parenteral feeding with sugar must therefore be recognized.

The possibilities which may be worth investigating to offset these disadvantages are the following:

1. Whether small doses increase the nitrogen output.
2. Whether a few doses may bring about accommodation.
3. Whether the dextrose that is given may be worth the nitrogen that it costs.

6. Prospect.

A thorough investigation requires experiments with full-fed, insufficiently fed, and fasting animals. It should determine whether parenterally injected dextrose can build fat in the first, can complete the diet in the second, or can spare nitrogen or prolong life in the third. It is especially with respect to the first class that we confront von Noorden's notion, to the effect that there must be a special disturbance of the fat-cells in diabetes, or else obesity would result from their storage of the surplus blood-sugar as fat. We must learn by experiment whether in the normal, full-fed animal, the fat-cells necessarily store sugar as fat, merely because it is present in excess in the blood.

My experiments have been performed with all three classes of animals. They were planned on a rather extensive scale, and were broken into by animal diseases and other difficulties. The result is that the group is badly balanced; there are relatively too many experiments of some sorts and too few of other sorts. In most instances a complete nitrogen balance-sheet is not presented. Sufficient tests were carried through to give assurance that the nitrogen of the food remained fairly constant; if any unevenness in the excretion is due to variations in the food, it is apparently not sufficient to confuse the results of the sugar. For estimating the importance of various factors, there have been various control experiments, not only with untreated animals, but also with injections of salt solution and of all the common sugars in addition to dextrose. Several substances besides sugars were also used.

7. Experiments with Full-fed Animals.

The following experiments illustrate the effects of various sugars in single doses of varying size, in animals on an adequate fixed diet.

The results with Dog 17 from January 14 to 24 may be tabulated as follows.*

DOG 17.

Diet 400g. Lean Meat

Date	Treatment	G. Nitrogen of Urine (24 hours)	G. Nitrogen of Feces
Jan. 15		12.75	
" 16		14.04	
" 17		12.94	0.55
" 18		12.38	0.42
" 19		13.34	0.98
" 20	Subcut. injection of 85.5g. lactose (10g. per kilo).	12.46	0.65
" 21		10.16	0.4
" 22		17.61	
" 23		9.34	
" 24		12.1	

Summary for Dog 17.

The subcutaneous injection of 10 g. lactose per kilo caused a diminution of nitrogen excretion during the next 24 hours, but the increased excretion in the 24 hours following that, caused the net result to be an increased loss of nitrogen. This loss was followed by retention on the third day.

The results with Dog 18, from March 28 to April 4, and from May 28 to June 25, may be tabulated as follows (see pages 204 and 205).

* N. B. The tables here and in all other places correspond to the protocols, *i.e.* the nitrogen values for a given day represent the 24 hours *ending* that morning. When an injection is given, the result is seen in the values for the *next* day.

DOG 18.

Diet 250g. Bread-and-meat Mixture.

Date	Treatment	G. Nitrogen of Urine (24 hours)	G. Nitrogen of Feces
May 28		4.99	0.96
" 29		5.55	0.52
" 30	Subcut.injection of 7.88g. saccharose (1g.per kilo).	4.84	0.598
" 31		5.01	0.65
June 1		5.16	0.39
" 2		spoiled	0.83
" 3	Subcut.injection of 23.04g. saccharose (3g. per kilo).	4.48	0.47
" 4		4.34	-
" 5		5.65	1.28
" 6		5.5	
" 7	Subcut.injection of 38g. saccharose (5g. per kilo).	5.	0.796
" 8		5.55	-
" 11		omitted	0.36
" 12	Subcut.injection of 38.25g. saccharose (5g. per kilo).	4.83	0.6
" 13		4.95	0.64
" 14		5.98	0.45
" 15	Subcut.injection of 7.58g. maltose (1g. per kilo).	6.05	-
" 16		4.74	0.64
" 17		5.24	
" 18		4.71	0.365
" 19	Subcut.injection of 22.34g. maltose (3g. per kilo).	4.745	0.34
" 20		4.03	0.68
" 21		5.84	0.67
" 22	Subcut.injection of 38.25g. maltose (5g. per kilo).	5.05	0.36
" 23		5.4	0.166
" 24		6.51	
" 25		4.89	

DOG 18.

Diet 275g. Bread-and-meat Mixture.

Date	Treatment	G. Nitrogen of Urine (24 hours)
Mar. 28		5.82
" 29	Intravenous injection of 17.5g. dextrose (2g. per kilo).	5.33
" 30		4.9
" 31		5.14
Apr. 1	Intravenous injection of 4.18g. dextrose (1/2g. per kilo).	5.56
" 2		5.34
" 3		5.62
" 4		5.46

The results with Dog 21, from February 11 to 22, from April 5 to June 16, and from August 10 to 13 may be tabulated as follows.

DOG 21.

Diet 250g. Bread-and-Meat Mixture.

Date	Treatment	g. Nitrogen of Urine (24 hours)	g. Nitrogen of Feces
Feb. 11		4.53	1.08
" 12		4.73	0.69
" 13		4.93	0.52
" 14	Intravenous injection of 12.35g. dextrose (2g. per kilo).	4.56	0.28
" 15		4.82	0.62
" 16		4.6	1.03
" 17	62.5g. dextrose per mouth (10g. per kilo).	5.14	0.85
" 18		4.51	0.9
" 19		5.38	0.526
" 20		5.03	
" 21		4.8	
" 22		4.13	

DOG 21.

Diet 225g. Bread-and-meat Mixture.

Date	Subcutaneous Injection	G. Nitrogen of Urine (24 hours)	G. Nitrogen of Feces
Apr. 5		4.06	0.96
" 6		4.50	0.42
" 7	6.6g. dextrose (1g. per kilo)	4.41	0.43
" 8		4.72	0.4
" 9		4.15	0.52
" 10	13.06g. " (2g. " ")	4.16	0.39
" 11		4.34	0.45
" 12		4.95	0.44
" 13	12.85g. " (2g. " ")	4.02	0.51
" 14		4.18	0.58
" 15		4.09	0.47
" 16		4.02	0.31
" 17	20.8g. " (3g. " ")	3.88	0.34
" 18		4.86	-
" 19		4.37	0.52
" 20	26.4g. " (4g. " ")	4.16	0.21
" 21		5.68	0.3
" 22		4.84	-
" 23		5.26	0.9
" 24		4.8	-
" 25	32.48g. " (5g. " ")	4.86	0.45
" 26		5.07	0.507
" 27		4.30	0.39
" 28		4.07	-
" 29		4.22	0.46
" 30	6.83g. levulose (1g. " ")	4.985	0.537
May 1		4.17	-
" 2		4.27	0.93
" 3	13.6g. " (2g. " ")	4.27	0.4
" 4		4.25	0.39
" 5		4.48	0.44
" 6		4.19	0.4
" 7	20.22g. " (3g. " ")	4.468	0.46
" 8		4.96	-
" 9		4.48	0.72
" 10	27.58g. " (4g. " ")	3.84	-
" 11		5.83	0.51
" 12		6.83	0.6
" 13		4.58	0.16
" 17		4.645	-
" 18		4.85	0.32

DOG 21 (Continued).

Date	Subcutaneous Injection	G. Nitrogen of Urine (24 hours)	G. Nitrogen of Feces
May 19		4.41	0.57
" 20	34.4g. levulose (5g. per kilo)	5.69	0.39
" 21		6.335	0.58
" 22		5.315	0.48
" 23		4.745	0.455
" 24	7g. galactose (1g. " ")	4.91	0.36
" 25		4.545	0.18
" 26		5.35	0.27
" 27	21g. " (3g. " ")	4.88	0.4
" 28		5.08	0.73
" 29		5.02	0.52
" 30	7g. lactose (1g. " ")	4.89	0.49
" 31		5.08	0.42
June 1		5.89	0.42
" 2		5.13	-
" 3	20.73g. " (3g. " ")	5.05	0.63
" 4		5.295	0.79
" 5		4.43	0.28
" 6		5.06	0.59
" 7	35g. " (5g. " ")	5.41	0.28
" 8		6.02	0.3
" 9		4.52	0.41
" 10		4.83	0.47
" 11		4.94	0.41
" 12		4.812	0.34
" 13	500cc. 0.85% NaCl Solution	4.72	0.47
" 14		5.45	0.53
" 15		5.05	0.735
" 16		4.35	-

DOG 21.

Diet 200g. Bread-and-Meat Mixture.

Date	Treatment	g. Nitrogen of Urine (24 hours)
Aug. 10		4.5
" 11	Intravenous injection of 100cc. 30% dextrose.	4.22
" 12		4.697
" 13		5.11

Summary for Dog 18.

The fall of nitrogen following intravenous injection of 2 g. dextrose per kilo on March 29 (page 205) is somewhat atypical, and may be due to renal injury.

Unchanged nitrogen output after ½ g. per kilo intravenously on April 1 is typical.

Subcutaneous injections of saccharose and maltose (page 204) failed to produce any well-marked rise of nitrogen excretion till the dose of 5 g. per kilo was reached in each case.

Summary for Dog 21.

The slight increase of nitrogen excretion after intravenous injection of 2 g. dextrose per kilo on February 14 (page 205) is probably typical. Likewise the intravenous injection of a little over 4 g. dextrose per kilo on August 11 caused a slight increase of nitrogen.

Dextrose 10 g. per kilo by mouth on February 17 did not increase the nitrogen output.

Subcutaneous injections of dextrose, not above 3 g. per kilo, increased the nitrogen excretion either not at all or to insignificant degree. Subcutaneous injections of 4 g. and 5 g. per kilo caused a slight increase.

Similar rules hold for levulose. It would appear that the nitrogen-increase from levulose is somewhat greater than from dextrose.

Galactose in dosage up to 3 g. per kilo had little or no effect upon the nitrogen.

Lactose caused a definite increase of nitrogen excretion only when the dose of 5 g. per kilo was reached.

The subcutaneous injection of 500 cc. saline solution on June 13 caused a slight increase of nitrogen output.

Conclusion. — There is relatively little difference between the sugars in their effects upon the nitrogen excretion. About 4 g. per kilo subcutaneously is the dose necessary for a distinct effect upon the nitrogen. The above dogs had been used for sugar-injections before, and there may be a slight question whether they had become less susceptible than normal dogs; but such a difference cannot be great.

The results with Dog 34 from March 25 to April 12 may be tabulated as follows.

DOG 34.

Diet 225g. Bread-and-Meat Mixture.

Date	Treatment	g. Nitrogen of Urine (24 hours)
Mar. 25		4.35
" 26		4.45
" 27		4.62
" 28	Intravenous injection of 37.5g.dextrose (6g.per kilo).	4.56
" 29		4.57
" 30		4.56
" 31	Intravenous injection of 12.9g.dextrose (2g.per kilo).	4.755
Apr. 1		4.57
" 2		4.32
" 3		4.51
" 4	Subcut. injection of 65g. dextrose (10g. per kilo) Intravenous injection of 12.9g. dextrose (2g. per kilo).	4.49
" 5		4.90
" 6		4.82
" 7	Subcut. injection of 50g. dextrin (8g. per kilo).	4.65
" 8		5.06
" 9		4.68
" 10		4.47
" 11	Subcut. injection of 19.2g. lactose (3g. per kilo).	4.37
" 12		5.25

Summary for Dog 34.

Intravenous injection of 6 g. dextrose per kilo on March 28 showed no demonstrable influence upon the nitrogen excretion.

Intravenous injection of 2 g. dextrose per kilo on March 31 was without effect upon the nitrogen totals.

The combined injection on April 4, of 10 g. per kilo subcutaneously and 2 g. per kilo intravenously, caused a pronounced increase in the nitrogen output.

The subcutaneous injection of about 8 g. dextrin per kilo on April 7 caused increased nitrogen excretion. The increase, therefore, may be produced by injection of colloids as well as crystalloids; and dextrin (or glycogen) has no advantage on account of its colloid nature.

After subcutaneous injection of 3 g. lactose per kilo on April 11, the nitrogen of the next 24 hours was slightly increased. As this dog was less accustomed to injections than the preceding members of the series, this result may possibly be nearer to the normal than those in the preceding dogs.

The preceding experiments show that sugar-injections above a certain figure increase the nitrogen excretion. But they also show that the quantity of albumin represented by this nitrogen is insignificant compared with the quantity of sugar thus received by the organism. The question therefore arises whether this surplus sugar may be stored as fat by an animal on full diet; whether hyperglycemia necessitates fat-storage in a normal animal; whether we thus are able perhaps to fatten an animal even against its will. Opposed to this possibility stand the notions of "sugar-intoxication," the emaciation commonly observed in sugar-injected animals, and the possibility that the animal receiving sugar may eat less.

Several feeding and injection experiments were performed, yielding crude results on this question. Nitrogen determinations were either not undertaken, or were spoiled by some accident or other somewhere in the series. Such analyses are therefore presented for only one experiment (Cat 15).

CAT 23.

Diet 100g. Horsemeat.

Date	Treatment	Initial & Final Weight, g.	Total Gain of Weight, g.	Average Gain of per day
July 12-18		1890 1960	70	10
July 18 to Aug. 18	Daily subcut. injection of 10cc. 80% Kahlbaum dextrose.	1960 2425	465	15
Aug. 18-25		2425 2475	50	7.
Aug. 25 to Sept. 11	Daily subcut. injection of 20cc. 50% Kahlbaum dextrose.	2475 2470	-5	-0.

Summary for Cat 23.

This was a small cat, in which a diet of 100 g. horsemeat wa above the requirement The cat gained weight on this diet fo one week preceding the injections. It continued to gain weigh

during one month of injections (July 18 to August 18). It continued to gain weight during the following week, in which injections were omitted (August 18–25) When the dose of dextrose was increased to 10 g. instead of 8 g., the gain of weight continued for a few days, but the final result for this period was a loss of 5 g.

It is questionable whether the injected sugar caused any deposition of fat. Certainly the moderate injections caused no emaciation or other sign of intoxication. Here, as always, an animal that eats holds its weight during dextrose injections. The effects when animals do not eat were shown in the previous chapter in a series of rabbits. The above statements apply to moderate doses. Excessive doses may presumably injure the animal otherwise than through its appetite. Such injury may be largely osmotic. The slight loss of weight in this cat when the dose was increased may be due to such injury.

CAT 26.

Diet 250g. Lean Meat.

Date	Treatment	Initial & Final Weight g.	Total Gain of Weight g.	Average Gain of Wt. per day g.
Oct. 1-19		1955 2540	585	30.7
Oct. 19 to Nov. 21	12 subcut. injections of 30cc. to 120cc. 10% Kahlbaum dextrose.	2540 2735	195	5.9

The above experiment was undertaken to test the effects of occasional as compared with daily injections. No benefit is observable from allowing a rest between injections.

But placing an animal on a fixed diet creates an artificial condition. A different and more natural condition is for the animal to govern its own eating during periods with and without sugar injections, under standard environment. Two such experiments were performed. Cat 46 represents injections on alternate days (doses 100 to 150 cc. 10 per cent dextrose solution). Cat 47 represents daily injections (doses 100 cc. 10 per cent dextrose). The records of these animals from December 25 to March 3 may be tabulated as follows. They were kept supplied with more meat than they could eat. On December 24, the weight of Cat 46 was 2530 g., and of Cat 47 was 2805 g.

Animal	Dec.25-Feb.12 Period before injections.			Feb.13-24 Period of injections.			Feb.25-Mar.3 Period after injections.		
	Av. Meat eaten per day g.	Gain in Wt. g.	Av. gain in Wt. per day g.	Av. Meat eaten per day g.	Gain in Wt. g.	Av. gain in Wt. per day g.	Av. Meat eaten per day g.	Gain in Wt. g.	Av. gai in Wt. per day g.
Cat 46 (Injections alternate days).	398.4	1615	34.4	227.5	-125	-10.4	389.2	350	50
Cat 47 (Injections daily).	296.1	765	16.3	150.	- 60	- 5.0	200	-130	-18

Summary for Cats 46 and 47.

Cat 47 for some reason showed a decline following the period of daily sugar injections. Otherwise, the record is that both cats lost weight during dextrose injections and gained weight when free from the injections. The gain of weight corresponds to the larger eating during the periods without injections.

Age is a factor of some importance in relation to the effects of sugar injections. This subject may be most conveniently treated in the next chapter, which is devoted to the effects of sugar in young animals.

The further question arises whether animals thoroughly accustomed to sugar injections behave any differently toward them than animals not so accustomed. The comparison made for this purpose between Cat 15 and his control, Cat 7, will, for the sake of unity, be postponed to the portion of this chapter dealing with the effects of sugar injections in fasting animals.

A comparison of two periods in the history of Cat 15, one without and one with dextrose-injections, may be tabulated here. The urine was passed spontaneously, except for emptying of the bladder at beginning and end of each period.

CAT 15.

Diet 200g. Meat daily.

Sept.25-Oct.19 (25 days). Period preceding dextrose injections.

Oct.20-Oct.31 (12 days). Dextrose injections alternate days, representing a total of 81g. dextrose.

	Total Urine cc.	Average per day cc.	Total N of Urine g.	Average Urinary N per day, g.	Total (dried) feces g.	Average (dried) feces per day, g.	Total N of feces g.	Average N of feces per day, g.	Total N Excreted, g.	Total N of Diet g.	N Balance
Sept.25-Oct.19	2475	99.12	160.63	6.42	88.	3.52	8.23	0.329	168.86	170.8	+1.9
Oct.20-" 31	1582	131.8	80.24	6.68	41.	3.41	3.44	0.287	84.68	81.98	-2.7

Summary for Cat 15.

In the period preceding the dextrose injections, nitrogen to the amount of 1.9 g. was unaccounted for, that is, was retained, or lost in hair or other ways.

In the period of injections, there was a nitrogen loss of 2.7 g.

Large sugar injections are never to be regarded as beneficial, and it is probable that some such figures as these will represent the actual effects of repeated injections upon the nitrogen balance. But this experiment is not a basis for positive conclusions, because of the evening temperature of 104 degrees on October 22, and the elevated morning temperatures of the three days following. No abscess ever developed, but such temperatures probably mean a slight infection, which would affect the nitrogen output.

On the basis of the tests to be reported among the fasting experiments, it is probable that previous habituation to injection has very little effect upon the behavior respecting nitrogen.

8. Experiments with Insufficiently-fed Animals.

One such series was composed of poorly-nourished puppies, and will therefore be described in the next chapter.

Only one experiment was carried to completion in adult animals. It comprised the following two cats.

Cat 33 had fasted from September 15 to October 15. Cat 40 had fasted from September 17 to October 10. The two were not identical in size nor in condition. Therefore one cannot be accurately compared with the other. A series of such animals was

proposed, but not carried through. Accordingly, the two records are mentioned here chiefly to set forth the peculiar outcome in Cat 33. They may be tabulated as follows.

Animal	Date	Weight	Diet	Treatment	Total N of Urine g.	Av. per g
Cat 33	Oct. 21-24	1920-1910	100g. Meat	0	13.81	3.
	" 25-29	1930-1935	" "	10cc. 100% dextrose injected subcut. daily.	16.16	3.
	" 30-31	1950-1900	150g. "	0	7.12	3.
" 40	" 21-24	2355-2305	100g. "	0	13.685	3.
	" 25-29	2300-2275	" "	0	15.68	3.
	" 30-31	2320-2310	150g. "	0	8.91	4.

Summary for Cats 33 *and* 40.

No conclusion will be attempted except that large subcutaneous injections of dextrose are not beneficial to an animal on insufficient diet. The impression was received that the injections were definitely injurious in Cat 33, which behaved more like a sick cat than like a starved cat.

When this experiment was ended, and the cats let loose in the room to eat their fill every day, the difference between the two was pronounced. Cat 40 regained weight promptly. Cat 33 regained a ravenous appetite promptly, and was, in fact, the hungriest cat in the room. But for some reason, the weight remained abnormally low. On November 24 the weight was only 1625 g., viz., less than during the above experiment. By December 29 it had slowly risen to 2210 g., but the cat was still abnormally emaciated. The animal was killed for obtaining blood, and the yield of blood, as forced from the carotid by the heart under ether anæsthesia, was greater than from any of a series of normal cats in excellent condition. Good circulatory strength seemed to be thus demonstrated.

The gross autopsy showed no anatomical cause for the condition. Microscopically, the organs were normal except the adrenals, the medulla of which showed the same picture of exhaustion as in advanced starvation. The question of causal relationships must be left open.

9. Experiments with Fasting Animals.

The first experiments pertain to the effects of certain injections upon the nitrogen output. Those with dogs will be presented first. The explanatory remark already made may be repeated, that in all such tables, the nitrogen in each instance represents the 24 hours ending that morning; the injection was given after catheterization, and the nitrogen of the *next* day shows the result.

DOG 17.

Weight 8490g.

Date	Treatment	N of Urine g.
Nov. 26	Starvation begun.	
" 29		2.73
" 30		1.64
Dec. 1	Intravenous injection of 1g.lecithin in 5cc.water.	Discarded
" 2		1.6
" 3	Intravenous injection of 5cc. 80% dextrose.	1.71
" 4		1.9
" 5	Intravenous injection of 5cc. 80% dextrose with 1g.lecithin.	1.6
" 6		1.44
" 7		1.41
" 8	Intravenous injection of 40cc. 10% dextrose.	1.72
" 9		Discarded
" 10		"
" 11		1.98
" 12		1.65
" 13		1.41
" 14	Subcut.injection of 61.5g. dextrose in 100% solution. (10g. per kilo.)	1.6
" 15		2.34
" 16		2.81
" 17		0.88

DOG 18.

Weight 8300g.

Date	Treatment	N of Urine g.
Nov. 25	Starvation begun.	
" 29		1.84
" 30		1.575
Dec. 1		1.68
" 2		1.27
" 3	Intravenous injection of 5cc. 80% saccharose.	Contamination with feces.
" 4		2.16
" 5	Intravenous injection of 5cc. 80% saccharose with 1g. lecithin.	1.49
" 6		2.185
" 7		1.78
" 8	Intravenous injection of 10cc. 40% lactose.	2.09
" 9		Discarded
" 10		"
" 11		1.46
" 12		1.75
" 13		1.8
" 14	Subcut.injection of 59g. saccharose in 100% solution (10g. per kilo).	1.85
" 15		1.22
" 16		4.1
" 17		1.79
" 18		1.55

DOG 19

Weight 8310g.

Date	Treatment	N of Urine g.
Nov. 27	Starvation begun.	
" 30		1.53
Dec. 1-2		3.3
" 3		1.54
" 4		1.26
" 5	Subcut. injection of 500cc. 10% dextrose solution.	1.65
" 6		2.06
" 7		3.39
" 8		2.18
" 9	Subcut. injection of 500cc. 0.85% NaCl solution.	2.23
" 10		2.68
" 11		1.77
" 12		2.
" 13		2.11
" 14	Subcut. injection of 500cc. distilled water.	2.22
" 15		3.75
" 16		4.24
" 17	Feeding begun.	4.71
Jan. 17	Starvation begun. Subcut. injection of 22.7cc. 80% dextrose (3g. per kilo).	
" 18	Subcut. injection of 29.2cc. 80% dextrose (3g. per kilo).	2.56
" 19	Subcut. injection of 28cc. 80% dextrose (3g. per kilo).	2.19
" 20	Subcut. injection of 46.5cc. 80% dextrose (5g. per kilo).	1.76
" 21		2.59
" 22		2.48
" 23	Experiment ended because of infection at site of last injection.	1.896

Summary for Dog 17.

The injection of 1 g. lecithin intravenously on December 1 did not increase the nitrogen excretion perceptibly.

The injection of 4 g. dextrose intravenously on December 3 (about ½ g. per kilo of normal weight) apparently increased the nitrogen excretion by a trifle (0.2–0.3 g.). The caloric value of the sugar is far greater than that of the albumin represented by this nitrogen.

The injection on December 5, of 4 g. dextrose with 1 g. lecithin intravenously, did not increase the nitrogen output, and if anything diminished it.

A large subcutaneous injection of 10 g. dextrose per kilo, on December 14, resulted in a pronounced increase of nitrogen excretion on the two succeeding days, with a diminution on the third day.

Summary for Dog 18.

The injection intravenously of 4 g. saccharose on December 3 caused a greater increase of nitrogen excretion than the same dose of dextrose in Dog. 17.

The addition of 1 g. lecithin to the 4 g. saccharose in the injection of December 5 failed to prevent the consequent increase of nitrogen excretion.

A large subcutaneous injection of 10 g. saccharose per kilo, on December 14, caused an increased nitrogen excretion, which made itself known only on December 16. There was no diminution thereafter.

Summary for Dog 19.

The subcutaneous injection on December 5 of 500 cc. 10 per cent dextrose solution was followed by an increase of the nitrogen excretion for the following two days.

The subcutaneous injection on December 9 of 500 cc. saline solution was followed by a very slight increase of nitrogen excretion for the following 24 hours. If the nitrogen for the 48 hours following the injection be averaged, there was no increase.

The subcutaneous injection on December 14 of 500 cc. distilled water was followed by the highest nitrogen excretion of all. Part of this can be accounted for by infection; but an increase altogether apart from infection can be safely affirmed.

The starvation experiment beginning January 17 ended in failure on account of infection. The nitrogen excretion, as far as

the experiment went, was larger in this dog which received dextrose injections than in Dogs 17 and 18, which received none.

DOG 21.

Weight 5600g.

Date	Treatment	N of Urine g.
Dec. 18	Starvation begun.	
" 19		1.47
" 20	Subcut. injection of 19.6cc. 80% dextrose (3g. per kilo).	1.43
" 21		2.03
" 22		1.16
" 23		1.39
" 24		1.2
" 25		1.4
" 26		1.85
" 27	Intravenous injection of 17.8cc. 80% dextrose (3g. per kilo).	1.79
" 28		1.83
" 29		2.1
" 30	Subcut. injection of 38.06cc. 80% dextrose (7g. per kilo).	2.52
" 31		1.61

Summary for Dog 21.

The subcutaneous injection of 3 g. dextrose per kilo on December 20 caused an increase of nitrogen excretion for the following 24 hours.

The intravenous injection of 3 g. dextrose per kilo on December 27 had a doubtful effect, aside from a little albumin in the urine. If there was any increase of nitrogen excretion, it was distributed over the next three days, possibly as a result of injury to the kidney. The injection was given more rapidly than advisable for the best nutritive effect.

The urine of January 1 was discarded because of diarrheal contamination. It would presumably have shown a nitrogen increase.

DOG 22.

Weight 6200g.

Date	Treatment	N of Urine g.
Dec. 18	Starvation begun.	
" 19		
" 20		1.47
" 21		2.18
" 22		1.32
" 23		1.07
" 24		1.76
" 25		1.51
" 26		1.35
" 27	Intravenous injection of 19.3cc. 80% saccharose (3g. per kilo).	1.24
" 28		1.07
" 29		1.69
" 30	Subcut. injection of 43.1cc. 80% saccharose (7g. per kilo).	0.91
" 31		1.85
Jan. 1		1.71
" 2	4.72g. dextrose per mouth (1g. per kilo).	0.77
" 3	9.4g. dextrose per mouth (2g. per kilo).	1.12
" 4	Subcut. injection of 5.9cc. 80% dextrose (1g. per kilo).	1.07
" 5	Subcut. injection of 17.25cc. 80% dextrose (3g. per kilo).	0.89
" 6		0.74
" 7	Subcut. injection of 55.62cc. 80% dextrose (10g. per kilo).	1.43
" 8		0.835
" 9		1.12
" 10		0.64
" 11	Subcut. injection of 52.8cc. 80% lactose (10g. per kilo).	0.94
" 12		0.645
" 13		3.4
" 14	Subcut. injection of 51.25cc. 80% saccharose (10g. per kilo).	1.
" 15		0.582
" 16		0.785
" 17		0.54

Summary for Dog 22.

The intravenous injection of 3 g. saccharose per kilo, on December 27, had less effect upon the nitrogen excretion than should have been expected. It is probable, however, that the figures of 1.07 g. and 1.69 g. for December 28 and 29 represent an actual increase, and that the excretion of 0.91 g. on December 30 is about the normal figure for this period. The delay frequently seen is illustrated by the lower excretion on December 28 than on December 29.

The subcutaneous injection of 7 g. saccharose per kilo on December 30 was followed by an increased excretion of nitrogen lasting 2 days.

The nitrogen excretion of January 3 and January 4 can perhaps be interpreted as a slight increase due to the feeding of respectively 1 g. per kilo and 2 g. per kilo of dextrose. At any rate, no nitrogen was saved.

The subcutaneous injection of 1 g. dextrose per kilo on January 4, and of 3 g. per kilo on January 5, were followed by an apparent diminution of nitrogen excretion. But this apparent diminution ended in the increased excretion of January 7 [for diuretic behavior of sugar see Chapter VI].

The subcutaneous injection of 10 g. dextrose per kilo on January 7 caused a small increase of nitrogen excretion for the ensuing 48 hours. This was very slight in proportion to the amount of dextrose injected.

The subcutaneous injection of 10 g. lactose per kilo on January 11 caused a marked increase of nitrogen excretion for three days thereafter.

The subcutaneous injection of 10 g. saccharose per kilo on January 14 caused an increase of nitrogen excretion only on the second day thereafter. The actual increase was slight, possibly because of exhaustion of the animal, which was now becoming decidedly weak.

The following dog was subjected to three equal fasting-periods, the initial weight in each of the three experiments being practically the same. The first period was plain starvation. In the second period, subcutaneous injections of 3 g. dextrose per kilo were given on the third and on the sixth day, to observe any possible differences in the effects at earlier and later stages. In the third period, subcutaneous injections of 3 g. dextrose per kilo were given daily.

Nitrogen analyses were in all cases performed daily. The totals are expressed in the following table.

DOG 57.

	Period I June 27-July 5 No injections	Period II July 14-22 Two injections	Period III Aug. 14-22 Daily injection
Weight at beginning	6860	6765	6800
Weight at close	5640	5175	5860
Total Nitrogen of Urine*	16.39	13.255	11.665

*The figuring of the N totals in each period begins with the urine specimen on the evening of the second day of starvation.

The high nitrogen excretion of the first period can partly be accounted for by the slight fever existing at the time (remains of distemper). But there is no such reason to explain the difference between the second and third periods. With the sugar, the animal excreted less nitrogen and lost less weight than without. The results agree with the findings of authors, for example Fichtenmayer, in rabbits.

The results, however, are atypical. The weight can be partly accounted for by retained water. The diminished nitrogen is contrary to what will be found in a majority of animals. The explanation in this instance probably is the age of the dog, that is, a puppy almost grown. The results then agree with what will be observed in the next chapter, viz., that sugar injections may act differently in young animals from the rule in adults. This is my only experiment with a fasting puppy. But it would be interesting to know if the possibility here suggested regarding young animals can be confirmed.

The next experiments concern nitrogen excretion in fasting cats.

CAT 49.

Date	Weight g.	Treatment	Total N of Urine g.	Average N per day g.
Oct. 21		Starvation begun.		
" 28-31	1790-1650		4.194	1.048
Nov. 1-4	1620-1560	Daily subcut. injection of 10cc. 80% dextrose.	4.15	1.04
" 5-6	1500-1475		1.275	0.638

CAT 171.

Date	Weight g.	Treatment	Total N of Urine g.	Average N per day g.
May 27		Starvation begun.		
June 7-10	2835-2670		4.97	1.24
" 11-14	2665-2535	Subcut. injection of 3g. dextrose per kilo daily.	4.27	1.07

CAT 172.

Date	Weight g.	Treatment	Total N of Urine g.	Average N per day g.
June 1		Starvation begun.		
" 2-5	2280-2100		5.88	1.47
" 6-9	2060-1860	Feeding begun June 9.	4.42	1.10
July 13		Starvation begun.		
" 14-17	2240-2110	Daily subcut. injection of 3g.dextrose per kilo.	3.72	0.93

CAT 56.

Date	Weight g.	Treatment	Total N of Urine g.	Average N per day g.
Dec. 5		Starvation begun.		
" 6-11	2600-2355	Daily subcut. injection of 3g.dextrose per kilo.	7.6	1.27
"12-16	2320-2075	Daily subcut. injection of 3g.dextrose per kilo. (Infection.)	6.59	1.32

CAT 57.

Date	Weight g.	Treatment	Total N of Urine g.	Total N per day g.
Dec. 5		Starvation begun.		
" 6-11	3115-2855		6.68	1.11
"12-16	2840-2655		3.73	.75
"17-20	2650-2490		3.64	.91
"21-24	2495-2380		3.39	.85
"25-28	2320-2320	Daily subcut. injection of 3g. dextrose per kilo.	3.29	.82
" 29	2210			1.33

CAT 58.

Date	Weight g.	Treatment	Total N of Urine g.	Average N per day g.
Dec. 5		Starvation begun.		
" 6-11	3330-3155	Daily subcut. injection of 3g.dextrose per kilo.	6.92	1.15
"12-16	3120-2890	Daily subcut. injection of 3g.dextrose per kilo. (Infection.)	6.25	1.25

CAT 59.

Date	Weight g.	Treatment	Total N of Urine g.	Average N per day
Dec. 5		Starvation begun.		
" 6-11	2960-2780	Daily subcut.injection of 2g.dextrose per kilo.	7.55	1.25
"12-16	2695-2540	Daily subcut.injection of 2g.dextrose per kilo.	4.4	.88
"17-20	2470-2265		3.64	.91
"21-24	2230-2195		3.7	.92
"25-28	2140-2075	Daily subcut.injection of 2g.dextrose per kilo.	3.	.75
"29-31	2060-2005	Daily subcut.injection of 2g.dextrose per kilo.	3.	1.
Jan. 1	1980	Injection of 6g.dextrose per kilo.		.72

Summary.

These injections were given by a helper, and infections were therefore unnecessarily numerous. The experiment with Cat 172 was interrupted by infection, and infection was responsible for the elevated nitrogen in the closing periods of Cats 56 and 58. Dextrose injections did not prevent the nitrogen-increase due to infection.

A sparing of nitrogen was apparent only in Cat 172, the value of 5.88 g. N without injections standing against that of 3.72 g. N for the corresponding period with injections. In general, the injections, if showing any effect, slightly increased the excretion of nitrogen reckoned on the body-weight. An exact calculation is probably not feasible, because of the influence of retained water upon the weight of the injected cats.

CAT 26.

ate	Weight g.	Treatment	Total N of Urine g.	Average N per day g.
ov. 22		Starvation begun.		
" 23-26	2690-2440	Daily subcut. injection of 200cc. 10% dextrose solu.	7.24	1.81
" 27-30	2385-2270	ditto	4.49	1.12
ec.1-4	2230-2065	"	3.57	.89
" 5-8	1925-1920	"	4.34	1.085
" 9-12	1945-1800	"	3.64	.91

Summary for Cat 26.

The cat was small, and was fat at the time of beginning starvation. The "normal" weight could not be placed at much above 2 kilos, so the daily injections would represent nearly 10 g. per kilo.

A mild infection probably occurred rather early, as indicated by the elevated temperatures in the mornings, when they should be nearly normal. The morning temperature of 104^6 on December 1 can mean nothing but infection, though the abscess was not found till December 12.

The nitrogen record is of interest, therefore, not for the increase which it shows, but as an example of how small the increase may be in the presence of sepsis plus maximum dextrose injections. Whether injected dextrose is ever of service in diminishing the septic increase of nitrogenous break-down is doubtful. Such large doses of dextrose are essentially harmful.

CAT 54.

Date	Weight g.	Treatment	Total N of Urine g.	Average N per day g.
Feb. 13		Starvation begun.		
" 14-17	3325-3030	Daily subcut. injection of 4g.dextrose per kilo.	9.99	2.50
" 18-21	3020-2870	Daily subcut. injection of 4g.dextrose per kilo.	5.98	1.49

Summary for Cat 54.

The right adrenal had been removed nearly a month before experiment. Nitrogen excretion was exceptionally high.

It is a question whether the preceding operation could explain such a result.

CAT 47.

Date	Weight g.	Treatment	Total N of Urine g.	Average N per day g.
Apr. 4		Starvation begun.		
" 5-8	3240-3080		5.05	1.26
" 9-10	3040-2985			
" 18		Starvation begun.		
"19-22	3180-2960	Daily subcut. injection of 3g. lactose per kilo.	5.65	1.41
"23-24	2885-2870		1.76	0.88

Summary for Cat 47.

The nitrogen determination for the urine of April 9–10 happened to be omitted. Comparison of the two periods, however, shows that, while the lactose injections may have increased the nitrogen excretion a trifle, the increase is very slight.

CAT 46.

Date	Weight g.	Treatment	Total N of Urine g.	Average N per day g.
Apr. 4		Starvation begun.		
" 5-8	3960-3610		6.68	1.67
" 9-10	3585-3490			
" 18		Starvation begun.		
" 19-22	3610-3430	Daily subcut. injection of 6g. lactose per kilo.	7.1	1.8
" 23-24	3345-3270		2.18	1.09
May 16		Starvation begun.		
" 17-20	3680-3450	Daily subcut. injection of 6g. dextrose per kilo.	7.71	1.93
" 21-22	3375-3300		2.66	1.33

Summary for Cat 46.

The large doses of lactose and dextrose increased the N-excretion. Here, as elsewhere, the increase from daily repeated doses is comparatively small; it is not a multiple of the increase produced by single doses.

In the following experiments with rats and guinea-pigs, the duration of life in starvation was the principal point of investigation.

RATS 12-18: Starvation.

No. of Rat	Treatment	No. of days starvation endured	Initial Weight g.	Weight on day before death, g.
12	One injection of 2½cc. 80% dextrose on day before death.	4	130	-
13	Daily subcutaneous injection of 2½cc. 80% dextrose solution with 0.5g. lecithin.	7	125	100
14	Daily subcut. injection of 2g. lecithin.	6	150	140
15	Daily subcut. injection of 4cc. 25% gelatin solution.	6	140	120
16	Control.	7	150	104
17	Daily subcut. injection of 2½cc. cottonseed oil.	12	140	97
18	Daily subcut. injection of 2½cc. 80% dextrose solution. (Site of one injection eaten out by rat).	8	170	125

GUINEA-PIGS 48-54: Starvation.

No. of Pig	Treatment	No. of days starvation endured	Initial Weight g.	Weight on day of death, g.
48	Daily subcut. injection of 30cc. 10% dextrose solution.	13	555	365
49	Daily subcut. injection of 30cc. 10% dextrose solution, & 1g. $CaCO_3$ daily by month.	13	540	338
50	Daily subcut. injection of 30cc. 5% glycerin solution.	7	495	415
51	Control.	14	390	203
52	Daily feeding of 60cc. 10% dextrose solution, half in forenoon and half in afternoon, also 1g. $CaCO_3$ daily.	12	486	284
53	Daily feeding of 60cc. 10% dextrose solution, half in forenoon and half in afternoon.	13	467	298
54	Daily subcut. injection of 30cc. 10% glycogen solution.	7	453	310

Summary for Rats 12 *to* 18.

Each rat was isolated in a small metabolism cage.

Life was not prolonged by subcutaneous injection of dextrose, lecithin, dextrose + lecithin, or gelatin. The rat receiving oil undoubtedly bore starvation best. But other experiments prove that the cause of the difference must have been in the rat and not in the oil.

Individual variations are noticeable. Thus Rat 12 died on the fourth day of starvation, after one dose of dextrose; while Rat 18 lived 8 days, and received five such doses of dextrose. Life was probably prolonged somewhat in Rat 18 by the eating out of one of the areas of injection by the animal.

Summary for Pigs 48 *to* 54.

Life was not prolonged by subcutaneous injections of dextrose, glycerin, or glycogen. Pig 49 received chalk by mouth while receiving dextrose subcutaneously, on the chance that any hypothetical acid intoxication might thus be overcome, but there was no benefit. Pigs receiving dextrose by mouth were also not benefited. The general impression was that all the treated pigs were injured by their treatment. Larger doses of dextrose would merely have brought death sooner. The control pig, which weighed the least, bore the starvation best.

An experiment with a young cat [Cat 19], mentioned in the previous chapter, also indicates the harmfulness of pure sugar feeding. After only eight days of starvation with dextrose feeding, the animal was in serious condition.

Two experiments were begun to test the effects of mouth-feeding of dextrose and starch respectively in adult cats. Both had to be abandoned as failures, in the case of dextrose because of vomiting and diarrhea, in the case of starch because of poor digestion. Cats are not suitable for such experiments.

The following fourteen cats belong in series, and are divided into two groups, according as they were starved to death or just to the verge of death.

Cats Starved to Verge of Death.

o. f at	Initial & Final Weight g.	Treatment	No. of days starvation endured	Total Nitro. of Urine g.	Nitro. of Urine per day per kilo of initial Wt. g.	Total Nitro. of Feces g.
8	2615 1640	Daily subcut. injection lactose 3g. per kilo, in 10% solution.	20	22.74	0.434	0.61
3	2800 1470	Control.	30	26.99	0.321	1.15
5	2150 1165	Daily subcut. injection of 30cc. 0.85% NaCl solution per kilo.	28	18.64	0.3096	1.34
9	2780 1585	Daily subcut. injection of saccharose 3g. per kilo in 10% solution.	24	26.65	0.406	2.69
0	2815 1635	Control.	22	25.27	0.408	1.06
1	3455 1995	Subcut. injection of cottonseed oil 250cc. Oct. 10. (One dose.)	39	39.066	0.289	3.92
4	2165 1630	Daily subcut. injection levulose 3g. per kilo in 80% solution. Infection.	11	12.25	0.514	0.44

Cats Starved to Death.

No. of Cat	Initial & Final Weight g.	Treatment	No. of days starvation endured	Total Nitro. of Urine g.	Nitro. of Urine per day per kilo of initial wt. g.	Total Nitro. of Feces g.
27	2945 1865	Daily subcut. injection of dextrose in 10% solution. Sept.16-Oct.10, 3g. per kilo Oct.11-14, 6g. " " Oct.15, 12g. " "	31	27.72	0.282	1.36
29	2425 1465	Same amount of dextrose as Cat 27, in 80% solution.	30	15.90	0.218	0.735
30	3015 1580	Daily subcut. injection cottonseed oil, 3cc. per kilo.	32	36.44	0.377	1.39
31	2665 1440	Control.	21	27.82	0.497	0.78
32	2600 1275	Daily subcut. injection of 80% saccharose solution. Sept.16-Oct.10, 3g. per kilo Oct.11-12, 6g. " "	28	30.42	0.4178	1.77
33	1470 940	Daily subcut. injection lactose 3g. per kilo in 80% solution.	14	12.47	0.6059	0.99
35	2290	Daily subcut. injection levulose 3g. per kilo in 10% solution. Infection.	11	12.70	0.507	0.22

Summary for Cats 18 *to* 45.

The records of the two levulose cats (44 and 45) are worthless because of infection.

The results in the two dextrose cats (27 and 29) are atypical. Such a great saving of nitrogen as is indicated in these two animals was never obtained in any other experiment. In Cat 29, extensive hydrops was found at autopsy.

The daily excretion of nitrogen, reckoned on the initial body weight, shows an increase in consequence of injections of saccharose and lactose (Cats 18, 39, 32, 43).

The low average nitrogen excretion in Cat 41 is atypical (due partly to the very long starvation), for oil injections do not spare nitrogen. But both the oil-injected cats (30 and 41) show that the oil did not increase the nitrogen-loss. Subcutaneously injected oil behaves practically like a non-irritating foreign body, and no reason is apparent why it should increase nitrogen excretion, as some authors have found it to do.

With respect to duration of life, the individual variations render judgment uncertain. For example, Cat 41 did not live longest because of any benefit from the oil, but because he was the largest and strongest cat at the outset. The dextrose cats (27 and 29) lived fully as long as could be expected from their general strength and nutrition. They were among the longest-lived of the series. The dextrose probably did not prolong life; neither did it shorten it. This result is chiefly due to the rather small dosage (3 g. per kilo). If large injections had been used, in the hope of supplying a large number of calories, life would undoubtedly have been shortened. The same result would have occurred from dextrose by mouth.

The concentration of solution used was without influence.

Probably the most important lesson from this series of animals is that dextrose, in suitable small doses, can be injected during starvation, and its beneficial effects upon the general well-being obtained [see later in this chapter], without shortening the duration of life.

It is of interest to learn whether accommodation may be developed; especially, whether animals accustomed to injections may utilize the sugar more advantageously than those not accustomed. For this purpose, an experiment was performed with Cat 15, an animal which had received dextrose injections for a

long period; and for control a female, Cat 7, as nearly similar to him as possible, was subjected to identical conditions in all respects, except for receiving no dextrose injections. The daily subcutaneous dosage in Cat 15 was 20 g. dextrose during the first fasting period and the feeding period, and 8 or 10 g. dextrose during the second fasting period. The comparisons between the two animals may be expressed in the following tables.

First Fasting Period, May 20–June 5.

	Weight at beginning of fast, g.	Number of days of fast	Weight at end of fast	Number of g.wt. lost
Cat 7 (Control)	3805	17	2870	935
Cat 15 (Injections)	3545	17	3250	295

Period of Feeding, June 5–July 2 (Identical diet for the two cats).

	Weight at beginning of period	Weight at end of period	Number of g. weight gained
Cat 7 (Control)	2870	3665	795
Cat 15 (Injections	3250	3985	735

Second Fasting Period, July 2–Aug. 10.

	Weight at beginning of fast, g.	Number of days of fast	Weight at end of fast	Number of g.wt. lost	Total Urinary Nitrogen July 10–Aug. 10
Cat 7 (Control)	3665	39	2075	1590	23.066
Cat 15 (Injections)	3985	39	2420	1565	21.635

Summary for Cats 7 and 15

In the first fasting period, the dextrose injections accomplished an unmistakable saving of weight. Throughout this period, Cat 15 was plumper and stronger than Cat 7; the latter gave the impression of a starving animal, while the former looked and behaved almost normally. The period came to an end because of the onset of ataxia in Cat 15. But at the time, he was stronger than Cat 7, and gave every indication of living longer, except for the nervous attack.

During the first of the feeding period, while Cat 7 was eating readily, the nervous condition created by the sugar injections caused some vomiting and lack of appetite in Cat 15. His appar-

ent gain of weight at this time was chiefly water from the injections. This difference may partly explain the fact that Cat 7 gained more weight during the feeding period than Cat 15. But the whole difference is not thus explained. In particular, it is evident that Cat 15 did not store fat in consequence of the sugar injections. Hyperglycemia therefore does not of necessity lead to fat-storage.

The second fasting period was longer, because of the later onset of ataxia. The saving of weight in Cat 15 in this period was only a trifle. His nitrogen excretion was a trifle less than that of Cat 7. Here again, his appearance of well-being stood in contrast to the cachexia of Cat 7, and he proved his superior strength by living, whereas she was too weak to rally, and died within 24 hours after feeding was begun. The difference in tenacity of life may have been merely a matter of individual constitution.

The conclusions to be drawn from the experiment are five.

1. There is no essential difference in the behavior of a cat accustomed to injections and the behavior already seen in cats not accustomed to injections.

2. Hyperglycemia does not necessarily compel fat-storage.

3. Dextrose injections, not too excessive, assist the general strength and well-being in a fasting animal, whether or not they save weight or spare nitrogen.

4. Dextrose injections in the quantities used do not spare nitrogen to any appreciable extent.

5. Dextrose injections are harmless. Cat 15 had long been subjected to intentionally excessive doses. The injections used in the present experiment were above the quantity therapeutically advisable. The nervous injury was due solely to excess. The important point is that after all the long course of sugar-injections, the ataxia, and everything else, Cat 15 still showed vitality superior to that of a normal cat chosen specially as being his apparent equal. The absence of any actual weakening effect from dextrose injections is demonstrated.

The query arises why animals die of asthenia, when they are supplied with an abundance of the sugar which supposedly supplies the fuel for muscles and, to some extent at least, for glands.

Statkewitsch found that in starvation the glands suffer earlier and greater changes than the muscles. He describes changes in the pancreas among other things.

Venulet and Dmitrowsky found exhaustion of the chromaffin substance in starved rabbits. They considered that this accounted for the terminal asthenia, and they claimed prolongation of life from administration of adrenalin.

Luksch found the adrenals normal in rabbits starved 10–14 days, and stated his opinion that if animals starved longer show adrenal changes, these changes are the results of the cachectic condition, not the cause.

It has been noted that the heart in starvation retains its glycogen more stubbornly than the skeletal musculature. Both liver and muscles cling to glycogen as if it were a substance of the highest importance to them.

Putting all such stray facts together, we may ask the following questions. Does death occur before the body-reserve is consumed (as Schulz proved) for the reason that certain glands, as pancreas, adrenals, or liver, are exhausted? Does such exhaustion involve loss of the power to store up glycogen from glucose? The power to form glycogen from sugar in starvation was demonstrated long ago. But I am not aware that anybody has ever determined whether this power is retained up to death.

The concrete question which can be answered in this connection therefore is: Under what conditions, as respects glycogen, do these sugar-injected animals die? Are they, at the end, unable to use the abundant sugar for forming glycogen, and perhaps for other purposes? Or do they present the anomaly of animals starving to death with an abundance of both sugar and glycogen at their disposal?

The question can be answered satisfactorily by killing a sugar-injected cat at that stage of starvation when it is unable or barely able to stand. Slow agonal changes which may partake of post-mortem character are thus avoided; and it is safe to assume that the condition which causes the extreme weakness of the entire body is the same which later causes death.

The following three experiments bear upon this point.

Cat 57; female; weight 3175 g.

December 5–23, starvation.

December 24–29, continuance of starvation with daily subcutaneous injection of 3 g. dextrose per kilo. December 29, ataxia, and death from calcium chloride injection.

Autopsy showed presence of considerable body-fat, and qualitative tests for glycogen in the muscles and especially in the liver were heavy.

Cat 59; female; weight 2985 g.

December 5 to January 1, starvation. In the periods December 5–15 and December 24–30 there was daily subcutaneous injection of 2 g. dextrose per kilo; on December 31 an injection of 6 g. per kilo was given, and another injection of 6 g. per kilo on January 1. January 1, bled to death when very weak. Blood-sugar = 0.85 per cent. Considerable body-fat. Liver yellow and oily with fat; microscopically, marked fatty infiltration. Qualitative glycogen tests of muscles heavy. Liver contained 4.4 per cent glycogen.

Cat 171; female; weight 3610 g.

May 27 to June 9, starvation.

June 10–14, continuance of starvation with daily subcutaneous injection of 3 g. dextrose per kilo.

June 14, very weak. Subcutaneous injection of 10 g. dextrose per kilo. Bled to death 2½ hours later. Blood-sugar = 0.585 per cent. Some fat still present. Muscle-glycogen = 0.52 per cent. Liver-glycogen = 3.6 per cent.

Half to three-quarters of an hour after death, there were remarkable muscle-contractions in this animal. The head, limbs, and trunk moved, the diaphragm and intercostal muscles contracted rhythmically, but the heart did not beat and the intestines were motionless. It is not known whether the high sugar-content had anything to do with the condition.

Summary for Cats 57, 59, *and* 171.

These examples show that cats in the last stages of starvation-asthenia, about to die of weakness, may be rich in both fat and glycogen. The liver-glycogen may be 3.6 or 4.4 per cent. The muscle-glycogen may be 0.52 per cent.

The spleen and the kidney under these conditions contained no glycogen. The latter finding may possibly speak a little against the belief that the cells of the convoluted tubules store glycogen from the sugar of the blood or urine.

Such animals will die of starvation, even though (as Schulz proved) their nitrogen-reserve is not exhausted, and though they have abundance of fat, glycogen, and sugar at their disposal.

Insufficient feeding with protein would undoubtedly have enabled them to live for a considerable time longer.

The chief question of all, which we are now in position to answer, is the following: Have parenteral dextrose injections any practical value, or any therapeutic use?

The answer to be given is affirmative. This is a place where my experiments should have been more numerous. This series is not as long as it should have been; but the observations seemed convincing, and the work at least presents a definite experimental method for arriving at a trustworthy conclusion.

Cat 40.

This animal had been on plain starvation since September 17. On October 5 he was becoming seriously weak. October 6–10 he received ascending doses of 1, 2, 3, and 4 g. dextrose per kilo by mouth. On October 10, starvation was ended, with the cat apparently stronger than when the sugar-feeding was begun. There is no evidence except the clinical appearances, but these seemed to indicate a very noticeable increase of strength from the sugar feeding.

Cat 33.

Starvation began September 17. On October 12, the cat was not only scarcely able to stand, but the rectal temperature had fallen to 95² degrees. In my experience, the following has been a rule without exceptions: A cat whose temperature has fallen to 95² degrees will die within 36 hours if left to itself, and if fed with lean or fat meat will die in less time than if fed nothing. This cat, in this condition, received a small subcutaneous injection of dextrose (1 g. per kilo), and the temperature rose to 98 degrees. The next day, $1\frac{1}{3}$ g. dextrose per kilo was injected; the morning and evening temperatures were 97⁸ and 96². The next day the injection was 3 g. dextrose per kilo; the temperatures were 99² and 100. The next morning (October 15), the temperature was 95⁸. An injection of 6 g. dextrose per kilo was given and meat was fed; part of it was taken willingly and part given forcibly. The cat survived, although, according to experience with other cats, meat feeding without sugar injection would not have saved life on October 12. The morning temperature of 95⁸ on October 15 probably indicates that by that time the reviving power of dextrose had nearly reached its limit.

The experiment furnishes tangible evidence, and also shows that the strengthening effects of dextrose are obtainable from subcutaneous as well as oral administration. Its benefit is not only that it strengthens the body in general, but also that it strengthens the digestive powers so that food by mouth can be used to better advantage.

Cat 41.

September 20, starvation begun.

October 28, cat unable to stand at all; refuses food; apparently dying.

10 a.m., temperature 95^{5}.

10:15 a.m., subcutaneous injection of 50 cc. 10 per cent dextrose solution. 50 g. meat fed forcibly.

12:30 p.m., temperature 94^{4}.

1:30 p.m., temperature 94^{7}.

2 p.m., subcutaneous injection of 5 cc. 100 per cent dextrose solution.

5 p.m., temperature 97^{2}. Appears stronger.

8:30 p.m., temperature 98^{9}. Decidedly stronger. 25 g. meat fed forcibly.

October 29, 9 a.m., temperature 95^{2}. 25 g. meat fed forcibly. 20 cc. 50 per cent dextrose solution injected subcutaneously.

12 m., temperature 98^{9}. 75 g. meat fed forcibly.

5 p.m., temperature 101^{5}. Cat sits upright in cage, and is able to walk. 20 cc. 50 per cent dextrose solution injected subcutaneously. 60 g. meat fed forcibly.

October 30, 9 a.m., temperature 99^{5}. Stronger. 3:30 p.m., 10 cc. 50 per cent dextrose solution injected subcut. 225 cc. milk and 100 g. meat fed forcibly during day.

5 p.m., temperature 103.

October 31, found dying. Autopsy shows viscera normal except spleen, which is large, black, and septic. Blood-smears show high leukocytosis and sprinkling of small cocci and diplococci; in the spleen these are mingled with bacilli. No pus anywhere; sugar-injections cleanly absorbed. Source of infection unknown.

Recovery would have been a more satisfactory outcome; but to live two days, and then have strength enough to react to infection with a temperature of 103 degrees and a large black spleen, is

sufficient evidence of improvement. The only question that can be raised against conclusions from this animal is whether the meat-feeding alone might have caused the improvement. I have had a sufficient number of other starving cats to furnish a positive basis for the answer, that meat-feeding alone cannot produce such effects. When a cat in the condition of this one on October 28 is fed forcibly with meat, the autopsy always comes a few hours later, and it shows the stomach dilated with meat and gas, and no sign of gastric juice or digestive action. In other words, motility and secretion of the digestive organs are both deficient. The cause of the hastening of death by meat-feeding in such cases is probably the mechanical or reflex effect of the enlarged stomach.

Dextrose given subcutaneously therefore not only strengthens the body in general, but by supplying the natural fuel to the smooth-muscle cells of the alimentary canal it enables them to perform tasks otherwise impossible. A similar improvement in the function of the digestive glands and the nervous or other mechanisms governing digestion and absorption is probable. The net result is that the animal's life may be saved.

Cat 26.

This cat was brought to the laboratory so weakened from privation and exposure that there was a question whether she would live. During thirteen days appetite and strength were very low, and only 120 g. weight was gained; the animal was apparently still in danger. Subcutaneous injections of dextrose on alternate days were then begun; the cat's strength visibly improved, and in 9 days 210 g. weight was gained. The prompt benefit apparently resulting from the dextrose might be attributed to coincidence. In any event, the harmlessness of the injections is demonstrated by examples of this sort.

The following example represents apparent benefit from dextrose in a hopeless case of general peritonitis.

Dog 59; bull terrier, age 3 years; weight 9800 g.

July 18, partial pancreatectomy, not to point of diabetes.
July 21, dog sick. Abscess under liver drained by operation.
July 31, dog apparently certain to be dead before tomorrow. Lies constantly on side, pays no attention to water, his wound, or

flies. The febrile temperature has sunk to 99⁸. Noon, subcutaneous injection of 500 cc. saline solution containing 30 g. dextrose.

August 1, 9 a.m. temperature 101. Dog sits up, licks wound frequently and vigorously, drinks and retains water. Wound explored, and general peritonitis with thin exudate found. 100 cc. 50 per cent dextrose solution was poured into peritoneum, with drainage which allowed escape of most of the fluid later.

August 2, dog still sits up. Subcutaneous injection of 500 cc. 10 per cent dextrose solution.

August 3, afternoon, death. Autopsy showed abundant thick pus in peritoneum.

In other cases like this, dextrose injections have sometimes seemed to show an unmistakable strengthening effect. In cases where the animal had a fighting chance, they have seemed sometimes to save life. I have been sufficiently convinced of their value to have adopted them as a routine for certain classes of sick animals. Like other clinical impressions, this can scarcely be proved by protocols, but requires confirmation by the observations of others.

As before mentioned, Kausch has claimed results of this sort in human patients. He has asserted that the effects of dextrose in dangerously weak patients are both more marked and more permanent than the effects of adrenalin given intravenously with saline. His statements have apparently gained little credence, doubtless because of existing notions concerning the "toxicity" of sugar and the increase of nitrogen excretion after sugar injections. My experiments lead me to agree with the general views of Kausch, and to commend the form of treatment which he has practiced. If erroneous ideas regarding "sugar-intoxication" can be set aside, the treatment will probably obtain a fair clinical trial. At any rate, I have here suggested an experimental method which can be made to yield convincing results. If a human patient turns for good or ill, there are many factors, and the change may be because of the treatment or in spite of the treatment. But when an animal, such as the cat, is starved to extreme weakness, the results of the dextrose treatment cannot be mistaken, at least if a sufficient series of individuals are used. If there is any "toxicity" in dextrose, this sort of animal is the one to show it. On the other hand, a gain of strength after dextrose

can be due to nothing else, for cats starved to the verge of death do not gain strength spontaneously.

My impression is that dextrose injections are highly beneficial to animals under these conditions. They will presumably be likewise beneficial to a certain number of human patients.

10. Therapeutic Use of Dextrose Injections.

This subject must be continued in the next chapter; therefore some statements concerning it will be left to the end, or repeated there.

For adults, it is probably rather immaterial whether dextrose is given dissolved in water, plain saline, or Ringer-Locke solution, though the last is to be recommended.

The purest obtainable dextrose should be used, but crude commercial glucose is perhaps better than nothing. The injection may be given either subcutaneously or intravenously. Kausch recommends the intravenous method especially. My experience has been chiefly with the subcutaneous; but since the publication of his work, if my experiments were to be done over, I should pay attention to the intravenous route. Intravenous injections must be given as slowly as possible, drop by drop, if it is feasible. The slower the injection, the more the patient can take without glycosuria and without harm.

Doses should be small. The object is not to see how many calories can be introduced. The doses used by Kausch represent the upper limits, but may perhaps be proper in extreme cases. Except for extreme cases, a dose of $\frac{1}{2}$ g. dextrose per kilo of bodyweight is enough for tonic effect. No dose ordinarily should be over 1 g. per kilo. It is better to repeat small doses than give too much at once. Doses should preferably never cause glycosuria, albuminuria, or other abnormal results.

Dextrose should be injected when needed, and only then. This does not mean to wait till the patient is dying, for injections should be given, like other treatment, in due season, and may be helpful when the patient is losing ground only a little. But the idea is, not to inject dextrose today on the chance that the patient may need it next week. If he does not need it today, wait till he needs it. The case is well exemplified in a starving animal. In such an animal, dextrose injections given day after day apparently lengthen life little if at all. There is no such thing as piling up a reserve of many calories by means of the repeated injections.

But when injections are given, the animal's strength and well-being are improved for that day and perhaps a day or two following. By waiting till the final weakening, the animal can be strengthened and kept up for several days longer. But if injections had been used from the first, an effect from them in the final stage could no longer be obtained. So also with a human patient; when he is actually weak and actually needs strengthening, dextrose may give strength. Through how many days it will continue to do so is unknown; perhaps for some weeks, if a small quantity of protein is taken by mouth, or for a shorter time on starvation. Protein is a better food than sugar [Magnus-Levy (4), p. 240]. But protein cannot be given parenterally. Dextrose given parenterally may perhaps save life on occasions when other food can be neither taken nor digested. But an injection of dextrose today will be of no service for a crisis coming a few days hence, unless some actual weakness is present today, and unless the added strength of today is needed to prepare the patient for the crisis to come. Dextrose injections furnish spending money, not reserve capital.

Kausch has already stated the principal indications and benefits of dextrose injections. They are of service in some of the cases in which transfusions of blood are used, and may supplement the latter, but will not replace them. In surgical practice, they may be given with benefit at any time, before, during, or after operation. Dextrose may be given subcutaneously or intravenously in the same solution with strychnin or adrenalin. In sudden shock or collapse, surgeons may yet learn to place their first dependence upon intravenous infusions of dextrose, supplementing it with adrenalin or other stimulants if necessary; the difference being that stimulants merely call out and use up reserve strength whereas dextrose adds new strength.

In medical practice, the use of dextrose is to answer the physician's prayer, "If I only had something to give this patient a little more strength, just for a few days!" Sometimes the strength is needed only for a few hours. For such cases, dextrose injections are worthy of conservative clinical trial, especially as they are harmless. Some possible medical indications for their use may be suggested, as follows.

In simple exhaustion. The reason why the patient's strength is spent is immaterial. Long exposure, cold or privation may have produced a condition from which rallying seems doubtful. Weiland (1) found diminution of blood-sugar even from muscular

weariness. Or the bodily powers may have given out after wasting disease, when the infection is practically overcome. A woman may be so far gone after labor as to render her immediate condition dangerous, or make her an easy victim for some slight hemorrhage or infection. A new-born child may be wavering between life and death. In these and all similar cases, there is no reason for omitting anything ordinarily done for such patients; but in addition, a small infusion of dextrose subcutaneously or intravenously may be worth trying. There is some reason to hope that it may sometimes be worth more than some of the measures now used.

In some cases of acute infections, dextrose injections may be of value. The frequency of hyperglycemia in fever and infection has been described by Hollinger, Lepine and Boulud (7), Tachau (1), and other authors cited in Chapter I. This hyperglycemia should be considered as part of a vigorous reaction. It probably represents the increased transportation of sugar to tissues that have to burn an increased amount of it. Hohlweg and Voit demonstrated the increased ability to utilize sugar in consequence of elevated temperature. Senator (2) and others have described the increased protein break-down in consequence of overheating; and F. Voit (1*A*) proved that the increase could be prevented by supplying enough carbohydrate. The heavy carbohydrate diet recommended by Shaffer and Coleman in typhoid is theoretically correct on these grounds; and the results are claimed to substantiate the theory. Favorable views are expressed by Crohn, by Gardner, and by Meara (2). It is not known whether dextrose given parenterally can diminish the protein-destruction of fever. Lesné and Dreyfus (2) have published affirmative experiments; but their results seem to cover only a few hours following intraperitoneal injection, and the nitrogen excretion is ordinarily diminished during this time, even though there may be an increase later [see Chapter VI]. At any rate, sugar is important for fever. Most aseptic forms of fever cannot occur without an abundant supply of glycogen in the liver. Naphthylamin fever is an exception [see Hirsch, Müller and Rolly, also Ott and Scott, etc.]. In infectious fever, the body can melt down its protein to form sugar for burning, but this involves metabolic labor and a sacrifice of valuable material, which may be saved by supplying the necessary dextrose. If digestion is feeble, protein may perhaps be given by mouth and dextrose subcutaneously. And especially at some

critical point, dextrose subcutaneously or intravenously might be life-saving. The function of even the isolated perfused heart is augmented by dextrose [see papers of Comessatti (1), Gayda, etc.]. The heart of a pneumonia patient may not improbably be strengthened by a supply of its natural fuel, and its reserve strength be taxed less than by other stimulants. The general strength may respond similarly in sepsis or other conditions. Kausch thinks he has saved life in puerperal septicemia by the use of dextrose. The great advantage of it is that it at least does no harm, and it works by feeding the tissues instead of using up reserve-strength like other stimulants; therefore whatever it accomplishes is clear gain.

Kausch has advised the use of dextrose injections in cholera. A certain amount of benefit should theoretically be gained. How far such benefit may extend in practice is an interesting inquiry. Since cholera patients now ordinarily receive large saline infusions, the addition of a suitable quantity of dextrose will be no inconvenience. The patients are weak or in collapse, therefore the nutrient and stimulating effects of dextrose are important. The patients need to retain water. As shown in Chapter VI, dextrose given subcutaneously causes retention of water; and as Pavy and Godden (2) have proved, it also diminishes the urine when given intravenously with sufficient slowness in suitably small quantity. In the presence of an abundant excretion of water through an injured bowel wall, it is possible that hyperglycemia may result in the passage of a little sugar from the blood into the intestinal lumen (Cf. Chapter I, section on intestinal excretion of sugar). The discussion of the influence of sugar upon bacteria in the intestine will be taken up in the next chapter. Here we may call attention in advance to the special advantages, theoretically at least, derivable from the use of sugar by mouth in cholera patients who can retain it. Three important factors combine to this end. First, so large a part is played in cholera by the growth and activity of the bacilli in the actual lumen of the bowel, as in a test-tube. Second, the cholera organism is one of those whose activities can be modified by the presence of sugar; and contrary to prevailing opinions, Kendall has proved that cholera bacilli ferment dextrose, lactose, saccharose, and various other sugars. Third, the cholera organism is rather susceptible to the harmful effects of acids, and is known to be easily overgrown by other organisms in culture. Therefore if the patient at any stage, but especially in earlier stages, can take and retain solutions of dextrose or lactose (or

or both), and perhaps can also take and retain tablets or cultures of sour-milk bacilli or any other vigorous organisms that can ferment dextrose or lactose with the production of an acid reaction, it is apparent that the chances are theoretically improved for a diminution of virulence of the cholera organisms remaining in the intestine, the restoration of a normal acidophile flora, and the disappearance of the disease. Strong sugar solutions might aid nutrition; but even solutions of 1 per cent should have a marked effect upon the bacterial activities, and should be retained as easily as water. These suggestions along the lines of Kendall's researches in intestinal bacteriology are still theoretical. The benefit of subcutaneous or intravenous injections of dextrose in improving the patient's strength has a more direct experimental basis. But neither can do any harm, and both are worth trying.

A field of pure experiment, of which nothing can be predicted in advance, is the use of dextrose injections for toxemic conditions, such as crises of exophthalmic goitre, pernicious vomiting, eclampsia, etc. It is to be remembered that dextrose given parenterally *must* be burned. No matter what becomes of other substances, the dextrose takes the right of way; it is bound to be burned. Whether its burning will assist the toxic condition or save any of the protein break-down is doubtful, but may be worth trying. The tendency of hyperthyroid patients to easy glycosuria is no contraindication, unless diabetes exists. Experiments like those of Rudinger and of Mayerle prove how efficiently carbohydrate spares protein in cases of hyperthyroidism, and the views of Landergren concerning the relations between sugar and protein katabolism perhaps lend some support to experimental attempts with parenteral sugar injections in this condition. In pernicious vomiting, the dextrose might help by supplying food; whether it would benefit the general condition is unknown. In eclampsia, it is common to give saline infusions, and the addition of dextrose will probably add strength, and might favorably affect the unknown toxic condition. Here again the treatment cautiously used may be expected to do no harm.

Another speculative field is opened up in the possibilities of sugar injections as antidotes for certain poisons. Rosenfeld in a series of articles has shown the frequent antagonism between fat and glycogen in the liver. Fatty livers generally contain little or no glycogen. The fatty liver caused by phloridzin, alcohol, chloroform, and similar poisons can be prevented by giving enough

glycogen-forming material, such as dextrose. The only exception in the list of poisons was phosphorus. Yet Manwaring concluded that the essential change due to phosphorus is increased metabolism of the hepatic and other body-cells; in the liver, glycogen is first destroyed, then fat deposited; when glycogen and other stores are consumed, the cell-protein is rapidly used up. Neubauer (1) confirmed some of Rosenfeld's results, and also found that the liver in phosphorus-poisoning, as in diabetes, can store glycogen from levulose but not from dextrose. He therefore recommended levulose feeding in the treatment of phosphorus poisoning. Neubauer and Porges attributed the results of phosphorus poisoning primarily to adrenal injury, and claim that adrenalin injections often prevent the fatty liver and glycogen-disappearance characteristic of phosphorus poisoning. Since parenteral injections of sugars cause an abundant formation of glycogen in both liver and muscles, furnish a large supply of combustible material, and influence metabolic conditions in some respects differently from sugars by mouth, the injections are worth trying for conditions such as those named. Subcutaneous injections of dextrose or levulose, or both, might be useful in phosphorus poisoning, chloroform poisoning, etc., and would be as good as anything else to try in acute yellow atrophy. These are cases in which the use of large and frequently repeated injections might be advisable, in order to keep the body flooded with available sugar.

Neubauer and Porges recommend rich carbohydrate diet in Addison's disease, on account of the customary hypoglycemia. Pitres and Gautrelet [see Gautrelet (4)] have claimed benefit in one case. But the weakness and other symptoms of this disease do not depend upon lack of available carbohydrate. My experiments [see Chapter XIX] agree with those of Porges, that no quantity of dextrose has any influence upon the symptoms which follow removal of the adrenals in animals. There is no sound clinical or experimental foundation for a carbohydrate therapy of Addison's disease.

Other limitations of the possibilities of dextrose should also be borne in mind. It will probably not modify the activities of bacteria in the fluids or tissues of the body. I have tried it in several dogs with peritonitis, by pouring different strengths of solution into the infected peritoneum; and while it has perhaps done no harm, it has seemed never to do any good. *In vitro*, such sugar solutions are highly unfavorable for infectious microorganisms, but conditions *in vivo* seem to be different.

We might hope that parenteral dextrose injections would remove acidosis, but there is no evidence that they will do so. Colombo proved that febrile acetonuria can be stopped or diminished by feeding sugar. Even a diabetic acidosis is, of course, benefited by sugar if the patient can utilize it. But Waldvogel found that subcutaneous dextrose injections, tested upon himself when on carbohydrate-free diet, did not check the existing acetonuria, but rather increased it.

Kittens taken from their mother too young, when they have just learned to eat and drink, will sometimes, after thriving for a week or so, begin to lose appetite and spirits, and slowly waste away and die. It might be expected that dextrose injections would have a stimulating and strengthening effect, but I have repeatedly found them without benefit.

In both canine and feline distemper, and in the snuffles of rabbits, dextrose injections are absolutely without value. Slow wasting conditions, therefore, seem not to be benefited.

Excessive injections are always harmful. I have a record of one cat with superficial ulcers, which was doing fairly well without treatment. Dextrose injections, sufficient for glycosuria, after a few days were followed by a change for the worse in the cat's general condition and the appearance of the ulcers. When the injections were omitted, the cat gradually improved. When they were resumed, conditions again became worse and this time resulted in death.

Concluding Remarks.

Leaving aside various incidental observations, the conclusions, which are chiefly negative, may be stated as follows.

1. Dextrose injections in full-fed animals indicate that hyperglycemia does not necessitate fat-storage. The evidence obtainable from the injection method is probably not conclusive; but, such as it is, it is opposed to the view that the obesity sometimes preceding or accompanying diabetes is due to hyperglycemia. The latter view is supported by no experimental evidence. Its underlying assumption, viz., that the fat-cells retain the power to utilize dextrose, more tenaciously than other body-cells, is essentially improbable, and is opposed by evidence to be presented in Chapter XIII.

2. It is not possible to fill out the diet of insufficiently fed animals by means of large subcutaneous injections of dextrose. Large injections are injurious.

3. In fasting animals, parenteral injections of dextrose and various other substances do not spare nitrogen. When administered day after day through prolonged starvation, they do not prolong life. They may even shorten life, perhaps by keeping temperature and metabolic activity on a higher level than in simple starvation. Likewise, the daily feeding of sugars and certain other non-nitrogenous substances apparently shortens life instead of lengthening it. Glycogen may apparently be formed from dextrose even in extreme inanition. Animals may die of weakness with an abundance of dextrose, glycogen, and fat in their bodies.

4. On the other hand, sugar is not a poison. In the daily dosage of 3 g. per kilo, dextrose and other sugars increase the nitrogen loss only slightly. The loss from daily doses is not a multiple of that from single doses. Nothing like a specific toxic effect of sugar is ever observed.

5. Trials under a variety of conditions have indicated only one field of usefulness for dextrose injections. In states of weakness, such injections seem to show a valuable nutritive and strengthening effect. Small doses, preferably a fraction of a gram per kilo, are worthy of clinical trial. With regard to the purpose and possible value of such injections, some speculative suggestions were made, the value of which can only be weighed by conservative experiment. It is believed that cats starved to extreme weakness are useful test-objects for judging the effects of such injections, and that the positive results in such animals, if confirmed, afford reliable evidence of benefit. The harmlessness of small doses of dextrose should justify careful experiments in human patients. In a limited class of cases, there is reason to hope for some genuine benefit from their use. If used indiscriminately in unsuitable cases, the method may fall into disrepute, and any possible value contained in it may be overlooked.

CHAPTER V.

EFFECTS OF SUGAR IN YOUNG ANIMALS.

In previous chapters, dextrose was found to be without specific toxic effect, and even beneficial in states of extreme weakness. Adult animals were used, and the possible modifying influence of age was left for consideration in the present chapter. Such consideration is necessary because of the possibility that sugar feeding or injections may be indicated in certain infantile disorders, and because of ideas introduced by Finkelstein concerning the toxicity of sugar. Finkelstein has since modified his opinions, but the influence of his original teaching is still felt.

Finkelstein (1, 2, 3) opposed the Czerny doctrine of the harmfulness of fat in infant feeding. At the same time, he carried to extremes certain earlier views concerning "food intoxication." Foods under certain conditions are supposed to poison the body. The poisonous action proceeds not from abnormal decomposition-products of the foods, but from the foods themselves. And to Finkelstein, the toxic food par excellence was sugar. These early papers of Finkelstein undertake to prove that albumin is harmless in any quantity. Fat is harmless for most babies, and when it is harmful, it acts only by fermentative bacterial processes, together with liberation of fatty acids, which injure the intestinal wall and render it more permeable for sugar. Not the products of intestinal fermentation or putrefaction poison the body, but the sugar. The intestinal wall injured by fermentative processes is supposed to become abnormally permeable to salts and sugars. The action of the two is considered identical; the "salt-action" of the sugars is a shibboleth. This action possibly depends upon a failure of the damaged intestine to "combine" the absorbed sugar in normal manner; the sugar thus circulates "free," poisoning the body and being excreted in the urine. Finkelstein described an alleged characteristic group of symptoms of this alimentary "intoxication"; two of the group were fever and mellituria. He looked upon sugars as "exquisite pyrogenous substances," blamed lactose especially for the poisoning of the system, and claimed instantaneous benefit and complete cure from the withdrawal of sugar.

Even small doses of sugar or of milk containing its natural sugar caused toxic symptoms, "with the certainty of an experiment." All signs of intoxication disappeared with the feeding of "Eiweiss-milch," a preparation containing a considerable percentage (1½ per cent average) of lactose, the very sugar which is alleged to be most toxic.

Schaps (1 and 2), a pupil of Finkelstein, reported experiments with subcutaneous injections. The solutions used were NaCl 0.8 per cent, dextrose about 5 per cent, and lactose about 9 per cent ("physiological" strength). The experiments were on nurslings; only one on a 10-year-old child. In infants, the threshold of sensibility was always above 1 cc., but never above 5 cc. Fever resulted equally from the same quantities of the three different solutions. Also, the same quantity of salt or sugar likewise caused fever when given in hypo-, iso-, or hypertonic solution. The first injection produces the strongest effect; this gradually dies away with repeated injections, till finally no fever results. Injection of any salt or sugar solution produces this "immunity" against all; there is no specificity. The effects do not occur in water-poor patients. They may be regarded as salt-effects. Others have shown that effects, interpreted as acidosis, follow the giving of either concentrated salt- or sugar-solutions by mouth. But Keller was unable to neutralize by giving alkali, and therefore speaks of them as salt-effects. Schaps attributes the fever in his experiments to a disturbance of the molecular concentration of the tissue-fluids. He interprets the results as supporting the position of Finkelstein, viz., as showing that fever in babies may be due to absorption of salt or sugar; it is not necessary to assume any action of bacteria or soluble toxins.

For some of the literature of this subject prior to Schaps, one may refer to Davidsohn and Friedemann (p. 43), also to the paper of Bingel. Also Köhler and Behr, in 1905, had reported that the injection of a little salt solution or distilled water, or the mere insertion of a needle with no injection, may cause a reaction resembling that of tuberculin, even though the patient is not hysterical. They also refer to Hutinell (Sém. méd., March 16, 1895) who stated that injection of physiological saline may cause temperature in tubercular children; to communications of Fürst and of Schmidt, concerning temperatures in hysterical patients from sham injections; and to a thorough investigation by Haak (Arch. f. exp. Path. u. Pharm., Vol. 38).

Leopold and Reuss confirmed Schaps' results; also Gofferje and Möllhausen.

Finkelstein and Meyer (quoted by Meyer and Rietschel) showed that 3 g. NaCl in 100 cc. water given by mouth may cause fever in young children. In children with nutritional disturbances, even 1 g. may cause fever.

Meyer and Rietschel in 1908 found that 60 per cent of infants, after subcutaneous injection of 20 to 50 g. physiological salt solution, reacted with fever, sometimes above 39 degrees. The addition of small quantities of KCl and $CaCl_2$ had a marked distoxicating effect; the pyrexial reactions became fewer and lower. Distilled water subcutaneously causes fever, but never by mouth. The salt therefore plays a part, but cell-injury is an important factor.

Meyer, in 1909, tried subcutaneous injections of a series of salts, testing the effects of substitutions of anions and kations. He concluded that both have an effect; and that salt-fever is an expression of the specific action of the sodium-halogen compounds.

Finkelstein (4) in 1909 stated positively that there exists no difference between the intoxicating or fever-producing properties of different sugars, lactose, maltose, saccharose, etc. "And it is possible, with the certainty of an experiment, by giving a dose of sugar (for example, 100 g. 12.5 per cent lactose solution*) to an infant with bowel trouble, to force up the previously afebrile temperature into a fever, practically with the same certainty as if one should give it a dose of tuberculin." The connection between bowel disturbances and the sugar of the diet is insisted upon as invariable. The part played by fat can only be secondary. The author emphatically rejects the fermentation theory of the injury from sugar, and upholds his theory of molecular injury, by salt-action of sugars. He finds supposed confirmation in the work of Schaps. He himself has found that fever results from giving not only sugar, but even physiological saline, to infants by mouth. His conclusions in favor of molecular or "salt" action, and against the fermentation theory, could not be more definite, positive, and emphatic than they are in this paper.

This doctrine ought to have found less following and more opposition among clinicians than it did find, because they know so many facts opposed to it. If sugars are "exquisite pyrogenous substances" acting through molecular disturbance, fever ought

* A large dose for a small baby.

not to be so strikingly absent in diabetes, ordinary alimentary glycosuria, and the hyperglycemia of nephritis and some other diseases. Neither could it be alleged that sugar absorbed through a damaged intestinal wall is more toxic than that absorbed normally. Robin, for example, found 83 cases of glycosuria among 1600 cases of intestinal disorder. This is the "dyspeptic glycosuria" of the French; but such glycosuria is altogether independent of fever. And, moreover, Cobliner (1) proved that in the very infants under consideration, those with dyspepsia and alimentary intoxication in the Finkelstein sense, the sugar-content of the blood is not increased. All these facts together should have disposed of the "sugar-intoxication" notion, merely from the clinical standpoint.

Friberger (1), Schloss (1), Cobliner (2), and Nothmann confirmed Meyer's statements concerning the pyrexial effects of sodium-halogen compounds. Nothmann found that not merely the youngest, but also older nurslings may react with fever after receiving 3 g. NaCl in 100 cc. water. But the condition of the bowel and of the nervous system are of importance in determining such a reaction.

Davidsohn and Friedemann studied the question in rabbits, in relation with anaphylaxis. They reported that rabbits sensitized with beef-serum behave like normal animals for about ten days. After that they behave differently, inasmuch as the saline injections, in smaller doses, cause higher and longer fever, and within fewer hours after injection, than in normal rabbits. The threshold dose for normal rabbits was 5 cc. or more of physiological saline; for anaphylactic rabbits 2 cc. Specially important in their work is the fact that intravenous injections of salt solution are less effective than subcutaneous injections. They were unable to obtain "distoxication" by addition of K or Ca. And, just as one should expect, they were able to cause the same type of fever with saline, dextrose, Ringer-Locke solution, and *serum of the same species* whether fresh or heated to 56 degrees. The whole research tends to discredit the notion of a special "toxicity" of any particular substance, and to emphasize the importance of the tissue-reaction in the organism, especially in a super-sensitive organism.

Rosenthal, in 1909, from the Czerny clinic, published experiments to confute the assailants of the Czerny theories. He found both in rabbits and in puppies that neither salt nor sugar (especially

lactose used) has any specific pyrogenic action. He sometimes found even hypothermia. In a series of animals he irritated the bowel with croton oil or fatty acids, to conform to Finkelstein's notions, and then fed sugar. He tried phosphorus poisoning, followed by doses of lactose, to study the influence of the liver; and also dogs with Eck fistula, to test the effects of absorption of sugar directly into the systemic circulation. His conclusions were against Finkelstein and Schaps. He declared sugar not to be the cause of fever in alimentary disturbances. Artificial lesions of the intestinal tract, or the other experimental conditions mentioned, do not give rise to alimentary fever after ingestion of salt or sugar. The author attacked the whole idea of the "salt-action" of sugars.

Friberger (2) reported that of 83 injections of physiological saline, 26 injections (in 12 children) resulted in elevation of temperature. Those suffering from disorders of nutrition reacted to doses of 10–30 cc. Larger doses were required for healthy children. Two healthy children and two others with eczema showed no fever after drinking NaCl solution, but cases of nutritional disorders sometimes reacted with fever, diarrhea, and collapse. The reaction to NaCl seems to cease at about the middle of the first half-year. Subcutaneously injected NaCl is more slowly excreted than that given by mouth. By neither route did the NaCl affect the nitrogen outfit. This difference holds also in older children and adults. The concentration of the solution is a factor in the rapidity of the excretion. The salt given in physiological solution is delayed in excretion. The author thinks that the salt causes the fever by injury to cells in the skin or bowel-wall, which give rise to pyrogenous substances.

Heim and John gave children NaCl solutions of varying concentration by mouth and subcutaneously. Temperature elevation is in their opinion due to a temporary insufficiency of water-excretion through the skin.

Schloss (2) drew several conclusions, one of which is, "Quick binding of salt or water in the infant organism leads to fever; quick elimination of salt or water leads to subnormal temperature."

Meara (1) presents a general statement of Finkelstein's earlier work and opinions, useful to those who do not read German.

Finkelstein and Meyer (1*A*, 1*B*) describing and recommending "albumin-milk," in an article 115 pages long (1910), fail to mention "sugar-intoxication" a single time. They here admit that

carbohydrate is a food of highest importance for the infant, cannot long be withdrawn safely, and must be restored to the diet as early as feasible, for increase of weight is generally impossible till carbohydrate is begun. [Following pages refer to 1*B*.] (P. 30) Sugar or easily assimilated farinaceous food should begin as soon as conditions warrant. (P. 73) Sometimes with older infants there is stationary weight even with abundant diet of Eiweissmilch; here it is necessary to add a carbohydrate, such as oats or wheat. (P. 75–76) In a very severe case it may be necessary to change from albumin-milk to woman's milk. A day of tea only should intervene, in order to keep separate the fermentable materials of the two diets. Especially the last proposal represents a great change, in attributing the damage to fermentation, and in admitting that woman's milk, with its sugar, may be better than albumin-milk, in the *worst* cases.

Finkelstein and Meyer (2) begin by ascribing intestinal irritation to abnormal fermentations. They describe casein as always harmless, and by its alkaline products opposing the acid fermentation. Fat is more dangerous, as Czerny correctly pointed out. But fat is harmful only in a bowel irritated by carbohydrate fermentation. Withdraw the sugar, and even larger quantities of fat than before will be found harmless. Lactose is at the bottom of the harmful fermentations. Therapeutic methods fail because the lactose in the diluted milk is sufficient to keep up the acid fermentation which prevents healing of the epithelium. Then, on page 1167, occurs the following: "Aus dieser Ueberlegungen heraus kamen wir zur Konstruktion der Nahrung, über die wir heute berichten, und die wir des hohen Caseingehalts wegen als 'Eiweissmilch' bezeichnen." They recite numerous indications for this albumin-milk. Though lactose causes diarrhea because of fermentation, yet the babies in question do well on dextrinized malt-preparations, etc., because these kinds of sugar are quickly absorbed and furnish little substrate for fermentation. Toward the close, the authors accept mother's milk as the best food of all. In the whole article there is not a word of "sugar-intoxication." It will be observed that the quotation given in the original German is inexact. Albumin-milk was *not* devised from considerations of intestinal fermentation, but on a molecular "sugar-intoxication" hypothesis emphatically opposed to the fermentation theory. Formerly the sugars absorbed were alleged to poison the system. But in the present paper, maltose and

dextrin preparations are recommended for the special reason that the sugars are very quickly absorbed. The acceptance of mother's milk as the best food is an admission that an ideal food may be rich in lactose. The authors' preference for albumin-milk as opposed to diluted natural milk is out of harmony with ideas of sugar-toxicity, because diluted milk may be made to contain no more sugar than albumin-milk.

Bingel made 110 injections of physiological saline in 85 persons. The doses were large, up to 500–1000 cc. in adults. He found in the majority a slight rise of temperature. Generally "immunity" resulted, but a few persons reacted with fever to each injection. Sugars likewise caused fever, lactose in a higher percentage of cases than dextrose. The author quotes Finkelstein, "dass diese Körper auf physikalischem Wege die Zellen funktionell schädigen, und damit die Möglichkeit abnormer Zersetzungen im Organismus schaffen, die ihrerseits zu einer Störung der Wärmeregulation Veranlassung geben." The author concludes that this is still the most probable view.

Helmholz (2) found that "5 per cent solutions of sodium chloride, bromide, and iodide, injected into rabbits subcutaneously in quantities of 10–25 cc., caused no rise of temperature in the great majority of experiments. Sodium chloride produces a slight rise in temperature when given in high concentration intravenously, and practically no rise when modified according to Locke. One per cent sodium chloride may in exceptional instances produce a febrile rise in temperature when given by mouth."

Cobliner (3) confirms the statement that NaCl solution can be "distoxicated" by addition of K and Ca. Hyperglycemia and leukocytosis occur in poorly nourished children after NaCl injection. Even in children who react to pure NaCl or pure sugar with high fever, there is no rise of temperature after injection of the following:

Dextrose	55.0
KCl	0.2
$CaCl_2$	0.2
$NaHCO_3$	0.1
Aq. Dest. qs.	1000.0

Freund found that rabbits not only fail to show salt-fever while fasting, but the character of the food and other factors

contribute to the prerequisite "disposition." Repeated injections did not produce "immunity." He confirmed Meyer's statement that other salts, especially calcium, can inhibit the fever due to sodium. Very small doses of morphin or other narcotics also suppress the fever. Anaphylactic animals and young children in a special condition of sensitiveness react more strongly than normal. Freund proceeds to call attention to the fact that salt injections are known to cause glycosuria as well as fever in rabbits. Adrenalin causes glycosuria, and a temperature curve which Freund finds to resemble that of salt. Calcium inhibits salt-fever and also adrenalin-glycosuria. Fischer proved that salt-glycosuria is of central-nervous origin, and adrenalin is supposed to excite the sympathetic. The author therefore tried experiments to extend this parallelism. Pilocarpin, which ranks as a stimulant of the "autonomic" nerves (opposed to the sympathetic), was found to prevent salt-fever, as anticipated. Also cholin, the antagonist of adrenalin and depressor of the sympathetic, prevented salt-fever. Freund's conclusion is that the "susceptible" condition is a state of increased sympathetic irritability, and that the salt exerts its effect through the sympathetic.

The above parallelisms are interesting. Yet it should be remembered that the thermic and glycosuric effects of salt are not parallel; fever is greater after subcutaneous than after intravenous injection, whereas glycosuria results only from intravenous injection. The analogy between the inhibition of salt-fever and the inhibition of adrenalin-glycosuria by calcium is open to criticism. The calcium added to salt solution is a mere trace, to make it more nearly isosmotic with the body-fluids. The calcium used to suppress the action of adrenalin is a considerable dose, which acts by depressing the nervous system. The trifle of calcium which prevents salt fever would have no effect upon adrenalin glycosuria.

Stuber reported a patient with true diabetes insipidus, in whom small doses of NaCl subcutaneously, or 30 g. NaCl by mouth, or even 2 g. calcium lactate, caused elevation of temperature, and repetition brought no "immunity." There was also an increased adrenalin-content of the blood, as measured by the Trendelenburg method. The author brings his findings into line with the opinion of Freund that salt-fever depends on a heightened sensibility of the sympathetic, and he suggests that diabetes insipidus may be

due to adrenalinemia, an increased function of the chromaffin system.

Freund and Grafe, using rabbits, investigated the metabolism in salt-fever. They gave subcutaneous injections of physiological saline, Ringer solution, and 6 per cent dextrose, in doses of 50–80 cc. Small doses of adrenalin were also tried. They note that even the introduction of a stomach tube can, by "shock," reduce the oxidation-processes of rabbits by 10–20 per cent. Their general conclusions are that salt-fever exhibits the two characteristics of infectious fever; (1) increase of heat-production; (2) increased protein metabolism. Concerning (1), the respiration experiments showed the greatest increase of CO_2 after dextrose, which, it is suggested, is perhaps due in part to burning of some of the dextrose. Hirsch and Rolly showed that aseptic fever cannot occur unless the animal is well supplied with glycogen; but the present authors made no tests with fasting rabbits. The height of fever produced was slight, from $\frac{3}{4}$ to $1\frac{1}{2}$ degrees, generally about 1 degree. The duration generally was only 2–4 hours. Concerning (2), it was found that the increased nitrogen for a 48-hour period amounted to 20 or 32 per cent. It should be noted that the authors here tried for high figures, by using large injections, of 3 per cent instead of physiological concentration, and giving injections twice daily. In this way the temperature was kept up to 40 degrees for six hours.

Schlutz, whose paper is most recent, worked at Finkelstein's suggestion, using rabbits. He reports a personal communication from Finkelstein, to the effect that the latter now believes that lactose acts by fermentation, injuring the intestinal wall and thus bringing about an abnormal metabolism of salts. Schlutz confirms Helmholz in finding fever after 3 out of 5 intravenous injections of distilled water, due to the liberation of pyrogenic substances from destroyed blood-cells. He gave lactose in varying concentration by mouth, subcutaneously and intravenously. In some of the mouth-experiments, β-oxybutyric acid or croton oil was used to irritate the intestine. The doses of sugar, as a rule, were large, up to 50 cc. of 50 per cent solution. Fever was slight, brief, variable, frequently absent. The author concludes that lactose possesses no distinct pyrogenic action alone, but may affect the temperature if given with a sodium salt (physiologic or Ringer solution) in a diseased intestinal tract.

Discussion. Experiments.

It is possible to form a clear and simple idea of the mechanism of the fever caused by salt or sugar. These substances under certain conditions injure cells, and the injured cells give off products which act upon the nervous system to cause fever. That the sugar or salt itself does not by entering the circulation cause the fever, is proved by the fact that intravenous injections of salt or sugar cause less fever than subcutaneous injections of the same; also by the negative results of Schlutz with lactose, all of which must circulate through the system until finally excreted by the kidneys. That products of injured cells cause the fever is well shown by the production of fever by injections of distilled water. The fever can be augmented or inhibited by agencies acting upon either one of the two parts of the mechanism, viz., the cells or the nervous system. When the cells are in any specially weakened or specially vulnerable condition, the reaction is easy to produce. When traces of potassium and calcium are added to the solution, the cells are injured less and the reaction generally prevented. Likewise, when the nervous system is in any specially excitable condition, the reaction is brought about more easily than normal. Anything that reduces the nervous excitability, as small doses of narcotics, suppresses the reaction. A specific toxicity of sugar does not exist.

Consideration may now be given to the import of these facts for the use of sugar in young children, (1) by mouth, and (2), parenterally.

1. Sugar by Mouth.

It might be regarded as immaterial whether the effects of sugar in infant diet receive explanation on the basis of molecular injury or on the basis of bacterial activity. It will occur to the mind that Finkelstein's albumin-milk has had just the same effect in the babies when he gave it on a molecular-injury hypothesis as when he has lately given it on an acid-fermentation hypothesis. But the important fact for infant feeding is, that the casting away of the sugar-intoxication hypothesis is also a casting away of all claims of any special or unique position for albumin-milk. Grant the sugar-intoxication hypothesis, and albumin-milk is what the Finkelstein school have claimed. Sugar is then a poison, and here we have the relatively sugar-free food. But discard the sugar-intoxication hypothesis, and substitute that of bacterial fermen-

tation, and immediately albumin-milk is merely one of many baby-foods, and must take its chances along with buttermilk, skimmed milk, gruels, dextrinized foods, and all the rest. It is then entirely a question as to which food may be best digested, cause the least fermentation, and give the best nutritive results. Finkelstein himself now admits the value of dextrins and gruels, which furnish the most sugar of all. With the dismissal of the "sugar-intoxication" error, the ground is cleared for a better appreciation of the high importance of sugar as regards (A) the metabolism and nutrition of the infant, and (B) the normal or diseased processes in his intestine.

A. Importance of Sugar in Infant Nutrition.

It is by no means agreed that albumin-milk is the best food for most cases of infantile nutritional disorders. The fact must be borne in mind that carbohydrate is of unusual importance in the infant's dietary, more so than in that of the adult, and should not be withdrawn except under absolute compulsion. Schaffer and Coleman have shown the benefits of heavy carbohydrate feeding in sick adults, and the benefits are far more important in sick babies, if carbohydrate in any form can be borne. Langstein states that the absolute carbohydrate requirement of the infant is not known; it should naturally be greater than that of the adult, for most of the protein intake must be used for growth rather than for transformation into sugar. Deprivation of carbohydrate leads to an earlier and greater production of acetone-bodies in children than in adults. A harmful influence of carbohydrate, according to Langstein, has never been proved except in connection with other foods. Finkelstein's later articles acknowledge the high importance of carbohydrate. He recommends adding it to albumin-milk as early as possible. Yet the albumin-milk contains $1\frac{1}{2}$ per cent of lactose, sufficient to prevent acidosis; and if lactose is as harmful for some babies as it is alleged to be, possibly some other food may be borne better from the outset.

Without attempting to follow all the clinical literature, it is evident that many pediatricians consider other foods better for most cases of nutritional disorder than the albumin-milk. Haverschmidt's experience is that after a short period of fasting, a gruel diet with increasing quantities of milk frequently effects a cure; this in spite of the doctrine of the harmful influence of

carbohydrate. Fever is common even with sugar-free diet. Often the carbohydrate diet resulted in the stopping of an existing glycosuria. There were no symptoms of intoxication from carbohydrate. Platenza states that only a few of his cases agree with Finkelstein's description. Many of them showed just the opposite behavior; that is, a diet rich in salt or sugar led to complete cure. Very seldom was there any relation between fever and the salt or sugar content of the food. The sugar in the urine was almost always of directly alimentary origin; after lactose the urine showed lactose, etc. Only twice was there a true glycosuria, and these were both fatal cases in the last three days of life, on water only. Lactosuria was also found in perfectly healthy children with no sign of intoxication. The author upholds the bacterial fermentation theory. Ritter and Buttermilch recommend buttermilk as the best food for intestinal and nutritive disturbances in the youngest infants, and for the most severe cases in older infants. Brady, although influenced by the "sugar intoxication" doctrine, nevertheless advocates Keller's malt soup for most infantile nutritional disorders, even when the condition has gone on to marasmus (decomposition). A search of the literature would doubtless yield more statements of this tenor.

B. Importance of Sugar for Normal or Diseased Processes in the Intestine.

On all sides, the bacteriology of the intestine, and the processes performed by bacteria in the intestine, are attracting increasing notice and receiving more thorough and intelligent investigation. Some of this work, pertaining to diabetes, must be discussed in the chapter on the oat-cure. In infant feeding, now that Finkelstein and his opponents are agreed that abnormal bacterial processes are at the bottom of the trouble, the intestinal bacteriologist stands as the master of the situation. The word "intoxication" now acquires a reasonable meaning. The intestine is the reservoir from which the poisonous products of bacteria, and sometimes the bacteria themselves, spread through the body and cause well-known forms of sickness. The laws governing such bacterial activity must govern the choice of food for the child. These laws are properly formulated, not by guesses or by empiricism, but by established principles of intestinal bacteriology. Clinicians will not fail to take interest in these principles, as soon as the knowledge of their existence has become general.

Finkelstein has assumed that acid fermentation is harmful, and that the alkaline products of casein are beneficial, by helping to neutralize acid. But two facts ought to be remembered; first, that no other bacterial products are so toxic as many of those produced in an alkaline medium; and second, that the normal intestinal reaction and intestinal flora of the infant are acid. The malt preparations which Finkelstein himself recommends give rise to an acid reaction. Hartje has lately published conclusions to the effect that the growth of acidophile bacteria is best favored by lactose and malt extract; and that the influence of these bacteria reduces putrefaction, improves the stools generally, and brings them into the condition of a healthy breast-fed infant's, in cases where they have been abnormal. Klotz (6) has similarly very recently emphasized the importance of the infantile intestinal flora. Both these authors seem ignorant of the priority of Kendall in this field. Kendall's paper of 1911 summarizes the work and conclusions of the author, and should be read by those interested in this subject.

Kendall adopts Alfred Fischer's distinction between fermentation and putrefaction. The former is the bacterial decomposition of non-nitrogenous substances, especially carbohydrates. The latter is the bacterial decomposition of nitrogenous substances, especially proteins. The opposition between these two processes is then pointed out. In the presence of carbohydrate, the reaction becomes acid, and the acid-forming fermentative organisms predominate over the alkali-forming, putrefactive types. The former and their products are relatively harmless and beneficial. The latter are the ones which produce poisonous metabolic products and also true toxins. Not only are pathogenic organisms fewer or absent in the presence of carbohydrate, but they themselves for the most part behave differently. Cramer and later Lyons [ref. by Kendall] analyzed quantitatively the bodies of pneumonia bacilli, Pfeiffer bacilli, and other organisms, and found wide variations according to the sugar-content of the media. The percentage of nitrogen-substance in the Pfeiffer organism was 62.75 per cent in 1 per cent dextrose medium, 58.8 per cent in per cent dextrose medium, and 45.88 per cent in 10 per cent dextrose medium. More important, along this same line, is the discovery of Theobald Smith (2), that the diphtheria bacillus can form no toxin in the presence of sugar. The same strain under identical conditions in absence of sugar forms abundant toxin.

Smith has later found a similar behavior in other pathogenic organisms. Smith further says, "We have no reason to believe that the action of diphtheria bacilli on mucous membranes differs from that manifested in cultures."

The studies of bacterial metabolism by Kendall and Farmer (also with Bragg and Day) are the most important that have been made in this field. By measurements of the ammonia and other products of bacterial activity, it is proved that a "sparing" action of carbohydrate for protein is fully as well-marked for most bacteria as for higher organisms. A majority of bacteria, including most of the pathogens tested, have very limited tendency to attack protein so long as available carbohydrate is present. The trifle of protein used in the presence of available sugar is probably only that needed for building the bacterial bodies. The entire energy requirement of the organisms seems to be supplied by carbohydrate. The lesson is that in the presence of available carbohydrate in the intestine, not only are pathogenic forms likely to be overwhelmed by harmless types, but they themselves are forced to make use chiefly of carbohydrate, and prevented from attacking the protein of the living cells of the intestinal wall. Kendall has also found that the products of bacteria in sugar-containing media are relatively harmless, whereas the products of the same bacteria in media identical except for the absence of sugar are highly poisonous. Other authors have witnessed a diminished virulence of bacteria when grown on sugar-containing media.

Kendall carried his own and others' results farther, in that he showed that the flora of the intestine can be controlled by the choice of food. The use of sour-milk bacilli as advocated by Metchnikoff and others is unnecessary. In human beings, monkeys, or any animals, a carbohydrate-free diet soon changes the character of the stools and of the flora throughout the length of the intestinal tract. The fermentative organisms largely disappear, and the obligate or facultative proteolytic types take their place. Let the diet be changed to carbohydrate, and the stools and the intestinal flora also change automatically. The proteolytic bacteria tend to disappear, and the acid-forming fermentative group flourish. The latter group are simply the normal flora of the healthy breast-fed infant. This flora can be produced in a person or animal of any age by merely choosing the right diet. Kendall showed that the organisms causing infantile diarrheas

especially the dysentery bacilli, belong to the proteolytic group, and their growth and toxin-production are both limited by the presence of sugar. A clinical application of these principles was begun, by feeding lactose to children with these diseases. Reports concerning the method will be found in the publications of the Boston Floating Hospital; the experience has been very encouraging, and the method is in growing use.

C. *Experiments with Excessive Sugar-feeding.*

If there is any specific toxicity in sugar, the fact should be discoverable by feeding sugar in excessive doses. Fermentative and irritative processes may also contribute, for it is possible to keep up a long-continued intestinal catarrh by means of repeated overdoses of sugar. Such experiments might be of interest from the following points of view:

1. The "sugar-intoxication" doctrine.

2. Diabetes and its complications. Results in adult animals have been negative; but it is possible that the young are more susceptible. It is desirable to know whether the continued hyperglycemia alone or in conjunction with the continued intestinal irritation may lead to any chronic glycosuric tendency. The doctrines of Finkelstein, concerning glycosuria in infantile disorders of nutrition, and of Funck and others, concerning the intestinal origin of diabetes, touch at this point.

3. Various nervous, developmental, and internal secretory disorders. In Cat 15 an interesting nervous and mental condition was produced by continued excess of dextrose; young animals might prove more susceptible, and possible light might be thrown upon nervous disorders of children, such as chorea or tetany. The supposed relations between parathyroids, tetany, calcium, and sugar were mentioned in Chapter III. A continued loss of calcium in feces and urine in consequence of repeated overdoses of sugar might be of some specific importance in the young organism. Rickets may be thought of in this connection; Schabad considers that some cases may be due to deficiency of calcium; Götting, by calcium-poor diet or oxalate feeding, produced bone-changes in young animals similar to but not identical with rickets; and reference has already been made to Hildebrandt, who holds the effects of overdoses of sugar to be an oxalate poisoning. The adrenals and adrenalin, supposedly important for sugar-metabolism, have

been brought into relation with rickets by Stoelzner and by Etienne, though the findings of Jovane and Pace have been contrary.

Dog 11; yellow pup; three-fourths grown; weight 3875 g.

This pup received about 15 g. saccharose per kilo by mouth every day for three weeks, with no other diet but bread and soup. The urine was seldom free from sugar, which generally was both saccharose and reducing sugar. With the prolonged hyperglycemia and diarrhea, no "sugar-intoxication" or other symptoms were observed. The pup remained in excellent spirits and gained weight. Mellituria stopped promptly upon stopping the sugar. The experiment was given up, in the belief that a pup of this age is too resistant for the purposes of the experiment.

Kittens 5, 6, 7, 8.

Black kittens at about weaning age, kept in separate cages, and constantly supplied with more meat and milk than they could eat. Beginning of experiment May 11.

Kitten 5, male; control. Initial weight 363 g. June 20, given away in healthy condition, weight 900 g.

Kitten 6, female; received $7\frac{1}{2}$ g. dextrose by mouth in divided doses daily. Initial weight 355 g. Death from weakness May 22; weight 290 g.

Kitten 7, female; received 5 g. dextrose by mouth in divided doses daily. Initial weight 336 g. June 20, weight 655 g.; daily doses of dextrose increased to $7\frac{1}{2}$ g. July 5, death from weakness; weight 715 g.

Kitten 8, male; received $2\frac{1}{2}$ g. dextrose by mouth in divided doses daily. Initial weight 332 g. June 20, weight 835 g. July 18, death from weakness; weight 740 g.

Summary for Kittens 5, 6, 7, 8.

Vomiting was always imminent with the large doses, and was avoided by distributing them in small fractions throughout the day. Diarrhea was continuous in the treated kittens. Temperatures were not taken. The urine was collected three times daily, and every specimen, except sometimes the first one in the morning, contained sugar. The untreated kitten grew well, and was given away on June 20. The others had no symptoms except

those due to diarrhea and diminished appetite. They presented the ordinary appearance of ill-nourished kittens. They did not conform to the Finkelstein picture, nor show any reduction of sugar-tolerance; for although diarrhea was intense and the kittens sick, whenever the sugar-feeding was stopped the glycosuria stopped also, in spite of milk diet. There were no nervous symptoms during life. Autopsy showed nothing except pot-bellied, ill-nourished little animals, with greatly enlarged mesenteric lymph-nodes. There were no bone-changes in any way resembling rickets. The organs were entirely negative in gross appearance. No microscopic examination was made.

2. Parenteral Sugar Injections.

Here we face the "intoxication" doctrine most directly; for here the sugars are introduced directly into the organism, and no fermentative processes can intervene.

A. Pyrogenic Action.

The first point to investigate is the alleged pyrogenic action of sugars. Preliminary observations upon a number of kittens and puppies during the first few days of life showed that the temperatures of these very small animals are so variable as to render them unfit for accurate experiments. The temperature (taken by rectum) varies especially with that of the environment, and also according as they are covered by the mother.

The following experiments were performed with somewhat older animals.

KITTEN 30 A; age five weeks.

Date	Weight g.	Temp.	Treatment
June 27	500	10 A.M. 99^{8}	
" 28	510	9 A.M. 99^{6} 5 P.M. 100^{2}	
" 29	510	10 A.M. 100 5 P.M. 98^{6}	At 11.40 A.M. injected 2cc.10% lactose solution subcut. Lactosuria present.
" 30	515	9 A.M. 99	
July 1	490	9 A.M. 100^{6} 5 P.M. 100^{4}	
" 2	500	9 A.M. 100^{8} 5 P.M. 101	At 11.30 A.M. injected 2cc.10% lactose solution subcut. Lactosuria present.
" 13	495	9 A.M. 100^{6} 5 P.M. 101^{2}	At 11.30 A.M. injected 2cc.10% lactose solution subcut. Lactosuria present.
" 14	490	9 A.M. 100^{4} 5 P.M. 100	At 11.30 A.M. injected 2cc.10% lactose solution subcut. Lactosuria present.
" 15	510	9 A.M. 100^{6}	Experiment ended.

Summary for Kitten 30A.

At and also after the time of taking the afternoon temperature on injection days, the kitten was excreting lactose. A "toxic" action of the circulating lactose was not manifested by any elevation of temperature.

The following are a group of puppies of the same litter, representing dextrose injections and controls.

PUP 1 B, Male, Mongrel.
Born in laboratory July 11.

Date	Weight g.	Temp.	Treatment
Aug. 1	740	5 P.M. 99 4/5	
" 2	760	10 A.M. 99 5 P.M. 100 1/5	At 11 A.M., 20cc. 10% Kahlbaum dextrose solu. injected subcut. Urine expressed at 12.30 & 3 P.M. It is scanty, and shows slight to moderate Benedict reaction.
" 3	780	10 A.M. 99 6/10 2 P.M. 99 5/10 6 P.M. 100 11 P.M. 99 6/10	At 12 M., 20cc. 10% dextrose injected subcut.
" 4	845	10 A.M. 99 8/10 5 P.M. 99 6/10	2 P.M., 20cc. 10% dextrose injected subcut.

PUP 2 B, male; mongrel.
Born in Laboratory July 11.

te	Weight g.	Temp.	Urine		Treatment
			Quant.	Benedict	
3. 1	900	2.45 P.M. 99 6/10			
2	920	10 A.M. 99 2/10 9 P.M. 100 1/10	Scanty	Heavy	40cc.10% Kahlbaum dextrose injected subcut. at 11 A.M. Urine expressed at 12.30 and 3 P.M.
3	970	10 A.M. 99 2/10 2 P.M. 101 2/10 6 P.M. 100 8/10 11 P.M. 100 2/10			At noon, injected 40cc.10% Kahlbaum dextrose subcut. Considerable struggle during injection today.
" 4	975	12 M. 100 4/10 5 P.M. 99 8/10			2 P.M., injected 40cc.10% Kahlbaum dextrose subcut.

PUP 3 B, female; mongrel.
Born in laboratory July 11.

Date	Weight g.	Temp.	Treatment
Aug. 1	750	2.45 P.M. 99.6	
" 2	770	10 A.M. 99 9 P.M. 100.3	
" 3	820	10 A.M. 100 2 P.M. 100.1 6 P.M. 101.4 11 P.M. 100	Injected 30cc.10% Kahlbaum dextrose subcut. at noon. Urine expressed at 2 & 6 P.M. Scanty. Moderate Benedict tests.
" 4	840	10 A.M. 99.8 5 P.M. 99.8	

PUP 4 B, male; mongrel dark brown.
Born in laboratory July 11.

Date	Weight g.	Temp.	Treatment
Aug. 1	630	2.45 P.M. 99.6	
" 2	660	10 A.M. 99 9 P.M. 99.5	10cc.10% Kahlbaum dextrose injected subcut. 11 A.M. Urine expressed at 12.30 & 3 P.M. More abundant than in pups 1 B, 2 B and 3 B. Slight or faint Benedict reaction.
" 3	705	10 A.M. 99.4 2 P.M. 100.5 6 P.M. 100.2 11 P.M. 99.9	At noon, 10cc.10% Kahlbaum dextrose injected subcut.
" 4	680	12 M. 100 5 P.M. 100.2	2 P.M., 10cc.10% Kahlbaum dextrose injected subcut.

PUP 5 B; female; mongrel; light brown.
Born in laboratory July 11.

Date	Weight g.	Temp.	Treatment
Aug. 1	500	3 P.M. 99^{4}	
" 2	500	10 A.M. 98^{8} 9 P.M. 99^{6}	Urine expressed 12.30 & 3 P.M. Paler and more abundant than in the other four pups. Benedict tests negative.
" 3	525	10 A.M. 99^{4} 2 P.M. 99^{3} 6 P.M. 99^{7} 11 P.M. 99^{5}	
" 4	590	12 M. 99^{6} 5 P.M. 99^{8}	

Summary for Pups 1–5B.

These pups, three weeks old, were given graded injections of dextrose solution subcutaneously. Even the largest dose failed to cause fever, although the glycosuria was heavy. The results were equally negative, whether only morning and evening temperatures were taken, or whether four records were made. The four-times-daily records were negative in Pups 1B, 2B, and 4B, in which they were taken on the second injection-day, just as in Pup 3B, in which they were taken on the first injection-day.

The following group represents lactose injections and controls, in a litter of six puppies only 9 days old.

PUP 1 A: male; mongrel; brown.
Born in laboratory July 2.

Date	Weight g.	Temp.	Treatment
July 11	450	10 A.M. 98^{2} 5 P.M. 99	
" 12	475	10 A.M. 100 5 P.M. 99^{4}	Injected 2cc.10% lactose solution subcut. 10 A.M.
" 13	525	10 A.M. 99^{1} 5 P.M. 100^{6}	Injected 2cc.10% lactose solution subcut. 12 M.
" 14	535	10 A.M. 98^{8} 1.30 P.M. 99^{3} 3 P.M. 99^{1} 4.20 P.M. 99^{6}	Injected 2cc.10% lactose solution subcut. 10 A.M.
" 15	600	10 A.M. 100^{4}	

PUP 2 A; male; mongrel; brown.
Born in laboratory July 2.

Date	Weight g.	Temp.
July 11	535	10 A.M. 99^{2} 5 P.M. 99^{4}
" 12	550	10 A.M. 100^{4} 5 P.M. 100
" 13	590	10 A.M. 99^{6} 5 P.M. 98^{2}
" 14	640	10 A.M. 98^{4} 1.30 P.M. 99^{3} 3 P.M. 99^{5} 4.30 P.M. 99^{6}
" 15	645	10 A.M. 100

PUP 2 A (Continued.)

e	Weight g.	Temp.	Urine		Treatment
			Quant. cc.	Lactose	
y 17	705	11 A.M. 99^9			At 11 A.M. injected 8cc.10% Kahlbaum lactose subcut. Placed in small cage for urine.
		12 M. 99^1	12 M. 3	6.4%	Allowed to nurse, alone and under observation.
		1 P.M. 99^9			Temperature taken shortly after finishing nursing.
		2 P.M. 100^1	2 P.M. Few drops	Heavy	Urine expressed.
		3 P.M. 100^5			Temperature taken while nursing.
			3.30 P.M. Few drops	"	At 3.30 P.M. injected 8cc.10% Kahlbaum lactose subcut.
		4 P.M. 99^7			Placed with the others to nurse.
		5 P.M. 100	5 P.M. 1/2	18.5%	Urine expressed.
		6 P.M. 100^2	6 P.M. Few drops	Heavy	Placed with the others to nurse
		7.30 P.M. 100^8			Isolated in metabolism cage again.
		9 P.M. 100^4			Has shown no ill effects whatever.
		10 P.M. 100	10 P.M. 2 1/2	8.1%	Urine expressed. Pup returned to mother for night.
18	705	9.30 A.M. 100^2	6	Mod.	Urine expressed.

PUP 3 A; male; mongrel; brown.
Born in laboratory July 2.

Date	Weight g.	Temp.	Treatment
July 11	415	10 A.M. 99^{8} 5 P.M. 99^{6}	Control
" 12	420	10 A.M. 101^{8} 5 P.M. 100^{5}	
" 13	475	10 A.M. 100 5 P.M. 100^{4}	
" 14	475	10 A.M. 98^{6} 1.30 P.M. 102^{8} 3 P.M. 103^{2} 4.20 P.M. 102	
" 15	490	10 A.M. 100^{2}	

PUP 4 A; female; mongrel; brown.
Born in laboratory July 2.

Date	Weight g.	Temp.	Treatment
July 11	500	10 A.M. 98^{7} 5 P.M. 98^{8}	
" 12	535	10 A.M. 102^{6} 5 P.M. 98^{8}	Injected 3cc.10% lactose solution subcut., 10 A.M.
" 13	560	10 A.M. 99^{6} 5 P.M. 100^{2}	Injected 3cc.10% lactose solution subcut., 10 A.M.
" 14	590	10 A.M. 98^{6} 1.30 P.M. 100^{6} 3 P.M. 102^{3} 4.30 P.M. 101^{8}	Injected 3cc.10% lactose solution subcut., 10 A.M. Injection site very tender.
" 15	560	10 A.M. 101^{2}	No infection; cause of yesterday's elevation of temperature unknown, unless it be the unusual pain and tenderness at site of injection.

PUP 5 A; female; mongrel; brown.
Born in laboratory July 2.

Date	Weight g.	Temp.	Treatment
July 11	475	10 A.M. 99 5 P.M. 99 2/5	
" 12	475	10 A.M. 101 6/10 5 P.M. 99 8/10	Injected 1cc.10% lactose solution subcut., 10 A.M.
" 13	495	10 A.M. 99 6/10 5 P.M. 99 8/10	Injected 1cc.10% lactose solution subcut., 10 A.M.
" 14	570	10 A.M. 99 6/10 1.30 P.M. 100 8/10 3 P.M. 99 7/10 4.20 P.M. 100 2/10	Injected 1cc.10% lactose solution subcut., 10 A.M.
" 15	580	10 A.M. 100	

PUP 6 A; male; mongrel; brown.
Born in laboratory July 2.

Date	Weight g.	Temp.	Treatment
July 11	535	10 A.M. 99 5 P.M. 98 8/10	
" 12	545	10 A.M. 101 4/10 5 P.M. 99 4/10	Injected 4cc.10% lactose solution subcut., 10 A.M.
" 13	610	10 A.M. 99 8/10 5 P.M. 100 4/10	Injected 4cc.10% lactose solution subcut., 10 A.M.
" 14	620	10 A.M. 98 2/10 1.30 P.M. 99 6/10 3 P.M. 100 7/10 4.30 P.M. 100 4/10	Injected 4cc.10% lactose solution subcut., 10 A.M. Injection site very tender.
" 15	630	10 A.M. 99 4/10	

Summary for Pups 1–6A.

These young puppies received graded injections of lactose subcutaneously, without fever.

The 3 p.m. temperature of 102°, in Pup 4A on July 14, might be claimed as an isolated positive reaction; but a control pup (3A) showed an elevation of its temperature on the same day, almost a whole degree higher. The slight fever of Pup 4A therefore cannot be attributed to lactose. In both pups it was probably due merely to excessive handling.

The experiment with Pup 2A, on July 17, the first injection this animal had ever received, followed by a lactosuria as high as 18.5 per cent, and no fever found in temperatures taken hourly, ought to be fairly decisive on this point.

B. Effects of Repeated Dextrose Injections.

The following were a litter of healthy kittens, nursed by their mother in normal manner. One served as control, another received dextrose subcutaneously, another received dextrose by mouth, and another received glycogen subcutaneously. Well-marked mellituria resulted from both the dextrose and glycogen injections.

KITTENS 9, 10, 11, 12.

June 17-July 5

No. of Kitten	Treatment	Weight June 17 g.	Weight July 6 g.	Gain in Weight g.
9	Control	302	407	105
10	Daily subcut. injection of 10-30cc. 10% dextrose solu.	265	337	72
11	June 17-29, control Weight on June 29, 380g., i.e. gain of 120g. in 12 days. June 29-July 6, feeding of 10-30cc. dextrose solution daily; some vomiting; gain in weight only 20g. in 7 days.	260	400	140
12	June 17-29, control. Weight on June 29, 321g., i.e. gain of 87g. in 12 days. June 29-July 6, daily subcut. injection of 10-30cc. 10% glycogen solution. Gain in weight only 4g. in 7 days.	234	325	91

Summary for Kittens 9–12.

Here the glycogen was obviously injurious, and the sugar probably so. Since the largest and strongest kitten of the four was chosen for control, and this one generally grows fastest, it is impossible to say whether there was any injury from the subcutaneously injected dextrose. The injections were purposely made large enough to cause well-marked glycosuria, *i.e.*, larger than they should ever be used therapeutically. Large dextrose injections in a thriving nursing infant could never be considered advisable. The essential point is that a very young animal, like Kitten 10, may receive repeated injections of dextrose through a period of three weeks, and grow and thrive during this time, with no evidence of "intoxication."

Pups 1B, 2B, 3B, 4B, 5B.

Litter born in laboratory July 11. Living with mother in normal manner, strong, fat, and thriving.

Experiment Aug. 2-Sept.5.

Animal	Treatment	Initial Weight g.	Final Weight g.	No.of g. Weight gained	Percentage of initial wt. gained
1 B	Subcut. injection of 2 to 4g. dextrose daily.	760	2075	1315	173
2 B	Subcut. injection of 4g. dextrose daily.	920	2060	1140	124
3 B	Control.	770	1920	1150	149
4 B	Subcut. injection of 1 to 4g. dextrose daily.	660	1920	1260	191
5 B	Control.	500	1480	980	196
Average for the 3 injected pups		780	2018.3	1238.3	158.7
" " 2 control "		635	1700	1065	167.7
" pups 1 B & 4 B		710	1997.5	1287.5	181.3

PUP 5 B.

Date	Treatment	Initial Weight g.	No. of g. Weight Gained	Percentage of initial Weight Gained	No. of g. Gain per day, Average	Percenta of initi Weight Gained per day Average
Aug. 2 to Sept. 5 (34 days).	Control	500	980	196	28.8	5.8
Sept. 5 to Sept. 24 (19 days).	Daily subcut. injection of 4g. dextrose.	1480	380	25.6	20	1.4

Summary for Pups 1–5B.

The size of the doses was not chosen for beneficial effect, but only to test what the effects of large quantities might be. Thus, most of the doses were such as to cause glycosuria; and for therapeutic use, injections ought not to cause glycosuria. No "toxic" action was perceptible. On the contrary, notwithstanding the excessive doses, an increased rapidity of growth in consequence of the dextrose injections here seems probable, on the basis of the following considerations.

1. The record of Pup 5B subsequent to September 5 is not a fair test, for sickness was already showing itself during this time; and on account of this sickness, probably distemper, the pup had to be killed on September 28. The impression was that the dextrose injections kept up the pup's strength longer than it otherwise would have kept up.

2. Among the five animals, Pup 3B, a control, was larger at the outset than Pup 1B or Pup 4B. At the end of the experiment, the three injected pups were the largest of the five.

3. The number of grams average gain by the injected pups was greater than that of the control pups. The percentage of gain was brought down by Pup 2B, in which the dosage was obviously too high. If we exclude this pup receiving an excessively high dosage, the average for the other two injected pups (1B and 4B) is considerably greater than the average for the two control pups, as respects final weight, number of grams gained, and percentage of gain.

4. The injected pups presented no abnormalities. They were not sluggish, nor pot-bellied, nor misshapen in any way, but were normal active pups.

5. In the case of Pup 4B especially, the injections seemed unmistakably beneficial; for this comparatively weak, listless animal, larger but less vigorous than Pup 5B, rapidly shot ahead, gaining in flesh and bone, till on September 5 it was as large and strong as Pup 3B.

The conclusion is that dextrose does not behave in young animals as a toxic substance.

There has been no success in rearing pups in the laboratory. They have prospered while nursed by their mothers, but after weaning have always done badly, irrespective of any experiments. The following are members of a litter born in the laboratory July 2. They were still with their mother; but the mother's milk had almost dried up, so they were chiefly on general diet of bread, milk, and a trifle of meat. Though retaining fair appetite, they were weak, emaciated, and in bad condition generally. The records may be condensed into the following tables.

PUPS 5 A & 6 A; Aug. 17-Sept. 2.

Animal	Treatment	Initial Weight g.	Final Weight g.	No. of g. weight gained	Percentage of initial wt. gained
5	Control.	1460	1690	230	15.7
6	Daily subcut. injection of 5g. dextrose.	995	1115	120	12.0

PUPS 3 A & 5 A; Aug. 17-Sept. 5.

Animal	Treatment	Initial Weight g.	Final Weight g.	No. of g. weight gained	Percentage of initial wt. gained
3 A	Daily subcut. injection of 5g. dextrose.	1080	2100	1020	94.4
5 A	Control.	1460	1620	160	10.9

PUP 5 A.

Date	Treatment	Initial Weight g.	Final Weight g.	No. of g. weight gained	Percentage of initial wt. gained
Aug. 17 to Sep. 5 (19 days).	Control.	1460	1620	160	10.9
Sep. 5 to Sep. 24 (19 days).	Daily subcut. injection of 5g. dextrose.	1620	2550	930	57.4

Summary for Pups 3A, 5A, 6A.

The tables mostly speak for themselves. The marked increase of weight from the dextrose injections is evident, whether an injected pup is compared with a control pup, or whether, as in the case of Pup 5A, a period of 19 days without injections is compared with a period of 19 days with injections. Pup 6A, which stands as an exception to this statement, had a broken leg during the latter part of the period, and was killed on that account on September 2.

The benefit from the injections should not be overestimated. The gain of weight chiefly showed itself as a pot-belly and a laying on of fat. An Homeric description of Pup 3A might be that "he indeed was big, but he had not strength according to his bigness." Nevertheless, it seemed that some increase of strength and well-being also resulted, and that animals lived which without the injections would probably have died. The doses were larger than should be used therapeutically, and smaller doses would probably give all the benefit obtainable and not lay on too much surplus fat.

These fattening results from subcutaneous sugar-injections in young animals are of a sort which cannot be duplicated in adult animals. The results are in harmony with the well-known high power of the young organism to utilize sugar. According to Moll, even a foreign albumin causes less disturbance in the young organism than in the adult. Reference may also be made to the single experiment in the preceding chapter, which seemed to indicate a greater nitrogen-sparing power of subcutaneous dextrose injections in young animals than is ever obtainable in adult animals. For convenience, the table of this experiment with a 10-month-old dog is reproduced here.

DOG 57.

	Period I June 27-July 5 No injections	Period II July 14-22 Two injections	Period III Aug. 14-22 Daily injecti
Weight at beginning	6860	6765	6800
Weight at close	5640	5175	5850
Total Nitrogen of Urine*	16.39	13.255	11.665

*The figuring of the N totals in each period begins with the urine specimen on the evening of the second day of starvatio

As previously noted, the higher nitrogen excretion of the first period may possibly be explained by a slight fever; but there is no such explanation for the ensuing periods.

Therapeutic Use of Dextrose Injections.

As formerly mentioned, Kausch has used dextrose in children, both subcutaneously and intravenously, with results over which he is enthusiastic. On advice of Kendall, babies with intestinal disorders have been treated in collapse with subcutaneous dextrose injections. The benefits from dextrose in suitable cases in adults have been suggested in the previous chapter. The following remarks are in order concerning its use in babies.

1. Dextrose is harmless. If the child receiving it receives no benefit, it should at least receive no harm. Exception to this statement may be taken on the basis of the publications regarding "salt fever," in which elevated temperature and more or less illness are reported in some babies in consequence of giving sugar or saline solution either subcutaneously or by mouth. Such information is useful. The testimony is unanimous that the ill effects from sugar are no greater than those from physiological saline solution. Ordinarily, nothing is regarded as more harmless than a saline infusion, and the same view seems warranted concerning a 5 per cent dextrose solution.

2. Sugar is probably best injected in about 5 per cent solution in Ringer-Locke fluid, or in some such formula as that recommended by Cobliner (3):

Dextrose	55.
KCl	0.2
$CaCl_2$	0.2
$NaHCO_3$	0.1
Ag. Dest. qs.	1000.

This is a more perfectly "balanced" solution, and therefore is borne without reaction by the very children who react to plain saline or dextrose solution with fever and malaise. In this way, even such risk as attaches to a simple saline infusion may be avoided. Kausch has given dextrose dissolved in simple saline, and has reported nothing unfavorable.

3. The dextrose solution may be given either subcutaneously or intravenously, as the physician may prefer. Slowness is the most important precaution in the intravenous procedure. The

flow should be drop-by-drop, or as near that as possible; the slower the better. Authors state that intravenous injections are borne by sensitive infants with less febrile or other disturbance than subcutaneous injections; but the latter method is often more convenient.

4. Infection is not to be dreaded. It was stated in former chapters, that with any sort of aseptic technique, isotonic sugar solutions do not cause infection. Saline hypodermoclysis is not omitted for fear of infection, and the danger with 5 per cent dextrose solution is no greater.

5. Doses should never be large, and especially at the outset are best made small. The treatment should properly be begun before a child is in too dangerous condition, as it is easier to keep a strong child strong than it is to make a dangerously weak one strong. By beginning early enough, the first doses may be made, if desired, as low as 25 cc. or less, in order to watch for any possible untoward effects. If there is any little elevation of temperature or other undesirable effect, it will be remembered that a few small injections ordinarily produce "immunity," so that later the larger doses can be borne without symptoms. Even the largest doses should be relatively small; they should never suffice for glycosuria, albuminuria, or any similar effect. Doses of $\frac{1}{4}$ to $\frac{1}{2}$ gram dextrose per kilo of body-weight are probably enough for any single injection.

6. How many days in succession the injections may profitably be continued, or how many injections should be given each day, can be decided only by clinical experience. Presumably a week or two of injections will do no harm. Two or three small injections per day may perhaps be better than one large one. Injections are an unnatural method of feeding, and should not be unduly prolonged. Nevertheless, no harm from repeated small doses has been demonstrated.

7. As between adults and infants, the latter, in animal experiments, utilize injected sugar to better advantage than the former. The therapeutic results should therefore be correspondingly better. Injections of dextrose are to be recommended in any form of infantile collapse or exhaustion. Its importance is greater in treating babies than in treating adults, because babies have less reserve food and less reserve strength to draw upon, and consequently, states of collapse are more frequent and more dangerous in them than in adults. Whether dextrose injections will be of

any service as a slight help in feeding babies who are merely chronically under-nourished, is a question that may be left open. It seemed of value in the ill-nourished puppies above described. It seems to build fat. But the true object is not to use maximum doses for the sake of depositing fat directly, but rather to use smaller doses, with the purpose of strengthening the entire organism, and therewith its digestive power. In the injected puppies, appetite seemed to increase. If the injections do not cause improved appetite and digestion in ailing babies, they have missed their best usefulness for the work of nutrition.

8. Let the purpose and value of dextrose injections be correctly estimated. They are an auxiliary method of feeding. In suitable cases, they may perhaps supply just the food that is wanted at just the time it is wanted. They keep up the sugar, an indispensable constituent of the blood, without the labor and the sacrifice of breaking down body-protein for the purpose. They probably will not modify the activities of bacteria within the body itself, but they strengthen the body-cells for the fight. They do not lower resistance; they raise it. Dextrose thus used is halfway between a food and a drug. Kausch compares its strengthening effect to that of adrenalin. And being a food, it presumably does not merely call out reserve strength like other stimulants, but contributes new strength. Its possibilities should not be overrated, and its indiscriminate use should be deprecated. In particular, patients who can take enough food by mouth generally need no injections. Theoretically, some benefit may be expected from dextrose in a limited class of patients, and it is to be hoped that conservative clinical experiments may justify these expectations.

In conclusion, repeated doses of dextrose have produced no specific toxic effects and no persistent glycosuric tendency in young animals. Under certain conditions the effects of dextrose injections have seemed to be beneficial.

CHAPTER VI.

DIURETIC ACTION OF SUGARS.

THE absence of a satisfactory definition or theory of diabetes mellitus is well recognized. The attempted definitions are confessedly nothing but statements of symptoms. So-called theories have swarmed and disappeared almost like ephemeral insects; but their own authors have generally acknowledged their inadequacy, and few of them have even attempted to strike at the root of the problem. Assertions that "the glycolytic power is diminished," or "the power of storing glycogen is lost," are fully coördinate with the quondam declaration that "nature abhors a vacuum." The scientific physical question is *why* nature abhors a vacuum; and the scientific physiological question is *why* certain powers seem to be altered in diabetes. A theory that is a theory must master this *why*.

The possibility has long been thought of that the sugar of normal blood is in some form of combination. This conception at present is far from being firmly established or generally accepted. But it is the hypothesis which seems to explain most satisfactorily a series of observations in the course of the present research. These observations have seemed to afford some ground for a simple theory and definition of diabetes. It will conduce to clearness and convenience if this proposed definition be stated plainly here at the outset.

Definition of Diabetes.

Diabetes mellitus is the condition resulting from a reduction of pancreatic amboceptor below the requirements of normal metabolism.

The word amboceptor is here chosen as having the best-defined meaning. Possible synonyms may be fixator, fixative substance, intermediary body, or anabolic substance. The idea is of a substance which enters into some sort of relation with food on the one hand and cellular protoplasm on the other, so as to

link them in some manner which permits assimilation, and without which normal assimilation is impossible. The relation may be one of vital or chemical union, solubility, adsorption, or anything else. In a broad general sense, the hypothesis of such an "anabolic" amboceptor substance is in line with Ehrlich's well-known hypothesis concerning food-assimilation, and views such as expressed by Biedl [(3), p. 14] concerning assimilative (and dissimilative) "hormones." It is similar to, yet different from, the hypothesis advanced by Cohnheim concerning the function of the substance furnished by the pancreas. Since the insufficient supply of this alleged substance (or substances) is the essential thing in diabetes, and all other things are secondary or accidental, the definition may be tersely stated as follows:

Diabetes is deficiency of pancreatic amboceptor.

The attempted support of this definition and of the claims made in behalf of it will be a matter of details comprising many chapters. For the purpose of the present chapter, it is necessary to follow in the literature lines of thought which converge from three directions, viz., the opinions and researches pertaining to —

1. The mechanism of the internal pancreatic function.
2. The free or combined state of the blood-sugar.
3. The diuretic effects of crystalloids and colloids, and the diuretic effects of sugars.

1. The Mechanism of the Internal Pancreatic Function.

Minkowski [(1), p. 94] stated that a satisfactory theory of diabetes was at that time impossible. Biedl [(3), p. 385] admits an undeniable fact when he says that the explanation has still not been given. But Minkowski as usual outlined the subject accurately. He suggested the two possible parts that the pancreas may conceivably play: either an action upon the sugar, or an action upon the cells of the liver and muscles. One suggested possibility [(1), p. 95] is that the pancreas perhaps acts upon the sugar-consuming organs in such manner as to "set free affinities, to which the sugar-molecule can attach itself."

The early notion, advanced especially by Lepine, that the pancreas supplies a glycolytic enzyme to the blood or tissues, is well known, but is not now accepted as an explanation of diabetes. A number of supposed mechanisms, such as the existence of diabetic sugar in some abnormal combination, or the destruction of "diabetogenous substances" by the pancreas, etc., may be

passed over without notice. That the pancreas has an oxidative function, and that the general power of oxidation is diminished in diabetes, was a common belief at one time but is now exploded. Nencki [quoted disapprovingly by Lepine (1), p. 154] said that the anomaly of nutrition in diabetics has nothing to do with processes of oxidation; and in a broad sense this is correct. Especially Baumgarten (1 and 2) has proved that the diabetic can burn perfectly a long list of substances closely related to sugar. A somewhat analogous suggestion is that of Stoklasa, viz., that among the "unknown substances" which the pancreas gives off to the blood, potassium is an important member; and that as a katalytic agent it is of the utmost importance in carbohydrate oxidation. The idea is based only on a remote analogy drawn from certain observations upon lower plants. In the dearth of other tenable hypotheses, this has gained a few followers. There is no real evidence in favor of it; and in Stoklasa's plants, the general oxidative processes were altered one way or the other, whereas in diabetes only the utilization of the dextrose molecule is affected.

The search for glycolytic enzymes in dead tissues has been persistent and unprofitable The status of this enzyme of blood was discussed in Chapter I. Various authors have claimed to find a sugar-destroying enzyme in various tissues. For work and polemic on this subject, the reader is referred to the papers of Stoklasa, Stoklasa and Czerny, Simacek, Feinschmidt, and Braunstein. Feinschmidt refers to the authors who claimed to find a diminution of glycolytic power in diabetic tissues. The pancreas in particular has been searched for the supposed enzyme, with slight and conflicting results, such as found in the reports of the above authors. Diamare and Kuliabko also claimed the presence of a glycolytic ferment in the isolated islets of Langerhans of fishes, but the claim was overthrown by Rennie (2) and withdrawn by Diamare (1*A*). Entirely new possibilities seemed to be opened up by the well-known announcement by Cohnheim in 1903. His claim was that although pancreas-extract and muscle-extract separately have very little glycolytic power, a mixture of the two destroys glucose much more energetically. The ferment was supposed to reside in the muscle (or other tissues). The pancreas was understood to supply an "activator," which was resistant to heat and thus distinguished from ferments. About the same time as Cohnheim, Hirsch (1*A*) published similar claims

regarding the action of liver and pancreas. A certain degree of confirmation seemed to be found in the work of Arnheim and Rosenbaum, and of Sehrt. Cohnheim's claims were supported by Hall; and Lydia Dewitt considered that atrophic pancreas-tissue, consisting largely of islets, possessed marked activating power. The convincing character of Cohnheim's first announcement is diminished by his later publications, which attempt to attribute serious errors and failures to trivial disturbing influences. Not until two years after his original publication did Cohnheim undertake to test the tissues of diabetic dogs by his method, with the result of failure to establish any difference from the normal.

Claus and Embden were the first to refute Cohnheim's claims; they attributed the results of the former investigators to bacterial contamination. The work has since been carefully repeated by McGuigan (1), Simpson, and others, always with negative results. Simpson especially concludes that numerous sources of error render reliable results by this method forever impossible. Taylor considers that different technique may explain different findings, and that Cohnheim's teachings may still carry some weight. Recently Vahlen has claimed to find in the pancreas a substance which accelerates alcoholic fermentation. More recently, McGuigan and v. Hess have further discredited both the ideas and the methods of the Cohnheim procedure. Milne and Peters (2) have found that the post-mortem tissues of depancreatized dogs destroy dextrose fully as actively as those of normal dogs.

As was pointed out in former chapters, all such methods deal with post-mortem phenomena. Every significant difference between the diabetic and the normal individual in this respect is abolished by death. And if any difference had been proved between diabetic organs and non-diabetic organs by the Cohnheim method, we might understand the interest in it as an alleged explanation of diabetes. But inasmuch as the pancreas and the muscle of diabetic patients will undoubtedly do post-mortem anything that non-diabetic pancreas and muscle will do, the bearing of Cohnheim's work on diabetes is hard to make out. Though I favor the general idea, viz., that the pancreas gives off something which renders possible the utilization of sugar and other foods by the tissues, I have no sympathy with any explanation of diabetes on the basis of enzymes in dead tissues.

Pavy [(1), p. 71] wrote in 1906: "Let it be supposed that the activator supplied by the pancreas is wanted to enable bioplasm

to take on, or to assimilate, sugar. It may be assumed that there is always a certain amount of it in normal circumstances distributed through the system and ready for use."

Frank and Isaac (4) believe that the pancreas furnishes a substance of amboceptor nature.

De Meyer (1, 4, 5) has drawn conclusions concerning the pancreatic function from post-mortem experiments. He finds that though the normal kidney secretes sugar-free urine with a glycemia of 1 to 2‰, the isolated kidney of the dog furnishes sugar-containing urine if the perfusion fluid contains 0.5 to 1‰ of sugar. Addition of pancreatic extract to the perfusion fluid reduces this glycosuria, and if the proportion is not above 0.3‰, a sugar-free urine can be obtained. Heger and De Meyer found that blood of depancreatized animals produces no glycolysis in vitro, but does so after addition of pancreas extract. Absence of the pancreas makes the kidney permeable for sugar, while addition of pancreas extract reduces this permeability. If pancreas extract be added to blood, and the liver of a depancreatized dog perfused therewith, the lost power of glycogen-formation returns. Therefore De Meyer (5) suggests that alimentary glycosuria in man with a normal percentage of blood-sugar may be due to a slight diminution of the internal secretion of the pancreas, this insufficiency giving rise to an abnormal sugar-permeability of the kidney. He believes the effect is upon the kidney, because dialysis experiments have proved the blood-sugar free. De Meyer (1) argues that the relation of the internal secretion of the pancreas to the glycolytic ferment is probably that of an amboceptor to a complement. De Meyer (3) concludes with the same idea: "Wir glauben auch, dass die Glykolyse, um ihre normale Intensität zu erreichen, eines Amboceptors oder einer Substanz bedarf, welche den Prozess fördert und von der Bauchspeicheldrüse herrührt."

2. The State of the Blood-Sugar.

Minkowski [(1), p. 95] suggests: "It might also be possible, for example, that sugar circulates in some loose combination, which protects it from attack by the oxidative processes; and that it is the duty of the pancreas to break up this combination and thereby make possible the normal oxidation of the sugar." The notion of Schmiedeberg, quoted by Naunyn (p. 469), is very similar; viz., that in diabetes the sugar has entered into some abnormal combination, by which it is protected from oxidation; levulose

does not enter into this diabetic combination, and therefore can still be burned in diabetes.

Phloridzin is largely responsible for the expression of views in favor of a normal combined condition of the blood-sugar. Lusk (see Stiles and Lusk) supposed that the phloridzinized kidney may have the power of splitting some particular dextrose compound formed in protein metabolism. Löwi first advanced the idea that all the blood-sugar is normally in combination, and that the phloridzinized kidney acquires the power of splitting this compound, thus causing glycosuria. Pavy claims priority on this point, but his statements were somewhat different.

In Chapter I was mentioned Lepine's common distinction between "immediate" and "virtual" blood-sugar. Part of the carbohydrate of the blood is known to be in protein combinations or other occult forms. The experiments concerning splitting with acids, by Lepine, by Pavy, and later by Finzi and numerous authors, all refer to the existence of this "virtual" moiety. Pavy (3) found that intravenously injected dextrose is quickly changed, so that part of the reducing power is lost, and reappears on boiling with acids.

Pflüger had in mind chiefly jecorin when he spoke of combined blood-sugar, and on this point he says [(1), p. 436]: "Soviel ich sehe, sind alle physiologischen Chemiker, die ihr Urtheil abgegeben haben, der Ansicht, dass die Frage noch nicht spruchreif ist. Es scheint sich um eine lockere Verbindung des Traubenzuckers mit Lecithin zu handeln, die vielleicht sogar in Dissociation ist." But Pflüger (12), though shattering by his criticism the attempted proofs of the free state of the blood-sugar, declares that he by no means considers the combined state of the blood-sugar as proved. Certain important facts of renal activity he himself explains on the basis of vital powers of the living renal epithelium, to which the laws of osmotic pressure play a very subordinate rôle.

Von Noorden [(3), p. 528] says conservatively: "Although upon various grounds it seems likely that the sugar does not circulate free in the blood, but perhaps in colloid combination and form, yet our present knowledge upon this point affords no firm basis upon which to found a theory of diabetes. Indeed, it is not definitely established that there is any difference between the healthy and the diabetic blood-sugar."

Magnus-Levy [(4), p. 75] says: "The 'living molecule' of protein in protoplasm, as the bearer of life, the instigator and

agent of all chemical changes, has to enter into a temporary alliance with the lifeless combustible substances, the dispensers of energy, in order to initiate and carry through their oxidation." Again (pp. 84–5), speaking of nitrogenous food-substances, he says: "It has been assumed from these facts that the bodies represented by the residual nitrogen are in a state of loose chemical combination with the bioplasm, such as exists between an enzyme and its substrate (or perhaps between a toxin and antitoxin). In this state they undergo certain chemical changes like hydrolysis or oxidation, such as would take place through the action of an enzyme. . . . According to this conception, then, the passage of the products of tryptic digestion through the mucous membrane is analogous to a continuous chemical process. The bioplasm acts as an enzyme, or collection of enzymes, to specific points by which side-chains are anchored; it keeps, furthermore, always saturated with side-chains, as is shown by the fact that residual nitrogen is the same during digestion as during fast. . . . This theory is analogous to that suggested by Verworn to account for the utilization of carbohydrates."

Eppinger and Falk have suggested a synthetic action for the pancreas; that it may combine dextrose with fatty acids, and the resulting compound may be what is actually burned.

Lepine is a believer in a combined condition of even the "immediate" sugar of the blood. Lepine [(1), pp. 207–9] describes the frequent discordance between glycemia and glycosuria, and explains it on the ground of both varying permeability of the kidney and varying degree of combination of the blood-sugar. One sentence is especially true for intravenously injected sugar: "If a large quantity of sugar enters the blood quickly, this sugar cannot all be immediately combined, and is eliminated as a foreign substance."

Herter (p. 373) says: "There seems to be little doubt that the greater part of the reducing substance of the normal blood exists as lecithin-sugar or some similar combination, and there are some writers who go so far as to claim that all the normal reducing substance exists in this form." And on page 377: "I believe the correct answer is that the cells do not burn sugar [in diabetes] because they cannot get at it in the form in which it is normally burned. In other words, it seems probable that in diabetics the difficulty lies, not in the oxidizing abilities of the cells, but rather in an impairment of the capacity of the cells of the body to prepare the sugar for oxidation."

Pavy has long upheld the idea of the combined state of the blood-sugar. He says [(1), p. 68]: "The suggestion presents itself that sugar is taken on as a side-chain by a proteid constituent of the blood and transported to the tissues, where it is taken off for subjection to utilization. The suggested operation is identical with what occurs in connection with the transport of oxygen." But this earlier opinion of Pavy refers to an occult, glycoproteid compound of sugar. On page 69 he says: "Loewi . . . has even gone the length of suggesting that the sugar, which is ordinarily looked upon as being in a free form in the blood, is in reality in a loosely combined state when the blood is circulating in the body. We did not commit ourselves to agreeing with this proposition." The definite statements of Pavy's ideas at that time are as follows.

Page 9: "Undoubtedly the carbohydrate must reach the tissues, but the great point in connection with the matter is as to the form under which the conveyance takes place. I will proceed to deal with the question, and I think it will be seen that it is quite incompatible with the circumstances existing that a small molecular body like sugar can constitute the medium for the transmission of food carbohydrate from the seat of absorption to that of utilization. Everything points to the impossibility of keeping the sugar molecule within the limits of the circulating current. When circulating through the kidney it cannot be prevented from escaping like other small molecular bodies and making its appearance in the urine. Impermeability of the kidney to sugar has been spoken of and suggested as a means of permitting sugar to reach the tissues without running off in the urine. I consider it may be confidently asserted that this suggestion has not a vestige of real support. No matter in what way the sugar reaches the circulation, it, in proportion to the extent that it does so, shows itself in the urine. The urine thus becomes an indicator of the state of the contents of the circulation as far as sugar is concerned."

Pavy (pp. 30–31) attempted incorrectly to explain the utilization of subcutaneously injected sugar on the basis of excessively slow absorption. Continuing (p. 32): "The difficulty has to be faced that the carbohydrate of the food has to reach the tissues, and that if it passed, as has hitherto been taught, through the circulatory system in the form of sugar, it would flow off in the urine as it does in diabetes."

Page 33: "Can the 500 g. of carbohydrate [in the Voit diet] pass through the circulatory system to the tissues in the form of free sugar without affording evidence of its doing so through the medium of the urine? . . . It is necessary for service in the economy that the food-carbohydrate should reach the tissues, but the transport must be in some other way than as free sugar in the blood, seeing that sugar passing to the tissues would at the same time pass to the kidney and filter off with the urine as it does in diabetes." Pavy next describes glycoproteids, and then says (p. 36): "I knew that carbohydrate underwent utilization in the tissues, and that a means of transport for it from the alimentary canal must exist that would not permit of its filtering off with the urine. The entry of carbohydrate into the construction of the proteid molecule I could see provided what was wanted, and gave the clue to the solution of the difficult problem that had confronted us. Locked up in proteid,

carbohydrate is in a safe position for freedom from being discharged with the urine, on account of the proteid molecule being too large to pass off by filtration." On page 111: "To what is this difference [between diabetes and the normal] attributable? I say it is due to the carbohydrate being assimilated — that is, synthesized into proteid and transformed into fat — at the seat of absorption, and supplementarily converted into glycogen and fat in the liver, in the one case and not in the other. If assimilated, it is prevented reaching the circulation as free sugar, and consequently does not reach the urine. If not assimilated, it reaches the circulation as sugar and thence flows off in conjunction with the urinary water."

The work of Bayliss on adsorption as preliminary to chemical reaction has interesting possibilities in application to assimilation of sugars and other foods. It is the basis of Pavy's present views, as expressed by Pavy and Godden (2). This belief concerns a fixation of sugar by "bioplasm" by means of adsorption. It is supposed to be carried out "by the lymphocytes and leukocytes of the blood, or bioplasm of any kind in a growing state with which the dextrose may be brought into contact." The essential truth grasped and defended by Pavy from the first has been the combined state of the blood-sugar, and the difficulty of retaining or assimilating the small dextrose molecule as such.

McGuigan and Brooks came to the conclusion that glycosuria is not determined by permeability of the kidney alone, but also by the condition of the blood-sugar; that this sugar normally is in combination with some large molecule, and that any free sugar passes very easily into the urine.

As previously mentioned, De Meyer (4 and 5), and Heger and De Meyer, consider that the internal secretion of the pancreas acts upon the kidney so as to render it impermeable to sugar; and they accept the results of dialysis experiments as proof that sugar exists in the blood in a free state.

The status of the dialysis method may be summed up in the three existing views regarding such experiments: (1) Dialysis experiments have proved that the blood-sugar is free; (2) Dialysis experiments have proved that the blood-sugar is combined; (3) Dialysis experiments have not proved anything concerning blood-sugar.

It is sufficient to begin the literature with Pflüger (12). Though not himself maintaining that the blood-sugar is combined, Pflüger devotes this article to destructive criticism of dialysis experiments especially those of Asher and Rosenfeld, who claimed to have proved that the sugar is free. Fresh beef-blood, with addition of sodium fluoride and toluol, was dialyzed against beef-blood that

had been made sugar-free by yeast. Disappearance of sugar from the fresh specimen was taken to mean that it had diffused through. But Pflüger argues that invertin from the yeast might have diffused the other way. Also, the authors dialyzed fresh blood against blood which had become practically sugar-free through standing 24 hours. Here yeast was absent, yet the fresh blood lost its sugar. But Pflüger holds that enzymes from the 24-hour blood may have diffused through into the fresh blood; and this applies not merely to the glycolytic enzyme, but perhaps also to some unknown enzyme, which may split off free glucose from its compound and thus render it diffusible.

Michaelis and Rona (2) took note of Pflüger's criticisms, and added a further criticism; viz., that if both free sugar and combined sugar exist in the normal blood, there is probably an equilibrium between them, and withdrawing the free sugar by dialysis will then gradually set free also the combined sugar. They undertook to determine the osmotic pressure of the free sugar in the blood without permitting osmosis to occur. For this purpose, their method was to dialyze fresh blood against salt solution to which was added an amount of dextrose equal to that in the blood. If any of the blood-sugar is not free, this method should presumably reveal the fact. By this well-planned arrangement, they determined that the partial pressure of the blood-sugar is precisely equal to the partial pressure of the same quantity of dextrose dissolved in salt solution. They therefore announced this as the direct proof that the sugar of the normal blood is free.

Edie and Spence published a quantitative method of blood-sugar determination based on dialysis. Under strict asepsis, they dialyzed blood against 0.9 per cent NaCl solution. They found the figures from dialysis consistently lower than those from the ordinary precipitation methods, and explained the difference as due to some sort of loose combination between sugar and albumin or lecithin in the blood. Dialysis of artificially prepared sugar-lecithin against salt solution yielded analogous results. They believe that the normal blood-sugar is perhaps in three forms, one free sugar, another combined sugar, and a third as polysaccharide or hydrolysible sugar. They claim that their method proves the corpuscles to be entirely devoid of sugar. As a method for practical use, it is claimed to be accurate; and though the time required for determination is longer, the actual work is much less than with the ordinary precipitation methods.

Lepine [(1), pp. 74–77] claims to prove by dialysis that the blood-sugar is combined. In long glass tubes he collects aseptically enough blood to yield about 60 cc. serum, centrifugalizes quickly, dialyzes the serum for two hours at 4° C. against salt solution, and then analyzes for sugar (1) the dialyzed serum, (2) the salt solution, and (3) a control sample of the serum kept at 4° C. without dialyzing. He thus claims to escape glycolysis by using serum instead of blood, and bacterial action by working at low temperature. Lepine asserts that if the serum is fresh, from a healthy animal, there is no sugar found in the salt solution, and the dialyzed serum contains the same percentage as the control. If the animal is not healthy, a certain amount of the sugar may diffuse through; and similar results occur after hemorrhage, intravenous saline injections, and other experimental procedures.

Lepine's brief procedure possesses some apparent advantgae over the 24-hour dialyses of other workers, as any compound of sugar may be less liable to break up. The absence of enzymes derived from the corpuscles may also be of importance. If the results claimed can be generally confirmed, the theoretical importance is obvious. The application of the method to diabetes would then offer special interest.

In discarding all negative results from dialysis experiments, it is not necessary to raise technical objections such as those of Pflüger. Two fundamental considerations suffice.

1. It is possible that the supposed blood-sugar combination is even looser than that of oxygen and hemoglobin. It may possess great biological importance and yet not be demonstrable by present physical or chemical methods.

2. More important is the fact that these methods use blood long after shedding. The sugar combined in the circulating blood may be free in the shed blood. Clotting may be prevented by suitable reagents, but these reagents do not prevent the formation of glycolytic and diastatic enzymes, which are non-existent in the living blood. Changes in the state of the blood-sugar from enzymic or other causes, would not be surprising under these abnormal conditions.

The conclusion is that any positive results from dialysis experiments necessarily possess interest. Negative results, though still interesting, have no binding force whatever in the question concerning the state of the normal blood-sugar.

In a previous chapter mention was made of Diamare's discovery that the blood of selachians contains normally no reducing sugar whatever. Nishi similarly found that the blood of tortoises is entirely devoid of dextrose. Even though Portier is said [see Chapter I] to have found minute traces of dextrose in selachian blood, the conclusion still seems unavoidable that the muscles of these animals normally receive their carbohydrate in some other form than dextrose. Possibly this form is similar to the "virtual" sugar of mammalian blood. It is possible that the "virtual" sugar of mammalian blood serves a physiological purpose, else why should it be there? And there is a further possibility that the muscles in diabetes may still burn "virtual" sugar though unable to use dextrose. But both Diamare and Nishi proved that the above animals, with normally glucose-free blood, show glycemia, even hyperglycemia, after extirpation of the pancreas. This is the important point in their work, to which it is desired to call attention in the present connection. If exact, it constitutes a positive demonstration of the occurrence of sugar in the blood in diabetes in a state different from the normal state. On account of the high theoretical importance, further information along these lines is desirable.

3. Diuretic Effects of Crystalloids and Colloids. Diuretic Effects of Sugars.

The diuretic effects of ordinary salts, and of bodies in general that possess osmotic properties, have long been recognized. The law established by v. Limbeck [ref. by Hedon (6)] fixes a relationship between the molecular weight and the diuretic activity. It is not necessary to go further into the literature. The work of Auteur may be mentioned, who used NaCl in experiments upon himself. He found, as would be expected, that increased salt ingestion leads to increased diuresis. The organism seeks to take up this loss of water by diminished output through bowel, skin, and lungs. The feces are dry and constipated during salt ingestion.

Concerning colloids, the earliest work by Heidenhain, Czerny, and others may be omitted. Spiro in 1898 published a few experiments along the same line, showing that the intravenous injection of colloids (gelatin and gum arabic) diminishes the urine and the lymph. Schmidt and Meyer noted not only glycosuria but also oliguria after injections of dextrin into the peritoneum.

Buglia made intravenous injections of gelatin in dogs. He found that the fatal dose was about 2 g. per kilo, and that death occurred in about 40 hours, with sopor, etc. Gelatin injections enormously increase the viscosity of the blood. Urinary secretion is greatly diminished or completely abolished. At the same time the viscosity of the urine diminishes, as also the electrical conductivity and the dry residue. After the injection there is a period of about an hour during which very little gelatin is excreted. Then comes a second period during which the gelatin excretion is high, and there exists a diminution or almost complete cessation of urinary secretion. A portion of the gelatin remains a long time in the body (beyond 40 hours).

One of the most complete works on the subject is that of Pugliese, a long paper with full literature. His conclusions are that gelatin and gum-arabic, as typical colloids, cause a marked diminution of urine. There is a large flow of liquid from the tissues into the blood; the blood is diluted and the lymph is diminished. A sufficient proportion of water in the injected solution overcomes these effects partly. NaCl, as a typical crystalloid, showed the typical crystalloid properties of increasing the urine and lymph, whether injected alone, or together with one of the above colloids. But the elimination of the salt is slowed by the presence of the colloid.

Ciovini published a confirmation and slight extension of the above work.

Knowlton, working with rabbits, found that injection of Ringer solution causes diuresis. The addition of gelatin or gum acacia to make an osmotic pressure about equal to that of the blood inhibits this diuresis. He proved that the inhibition is not due to a change of arterial pressure, nor to any poisonous action on the renal cells. The possibility that the inhibition is due to increased viscosity of the blood and consequent lowering of the capillary pressure, is ruled out by using starch solutions, more viscous than the gelatin or gum, but lacking the osmotic properties; the starch did not inhibit diuresis. The conclusion is that the efficient agent in the inhibition is the osmotic power; in other words, that the osmotic pressure of the blood is a factor in diuresis. This view is confirmed by the fact that the diuresis following chloride injection, and due to mere hydremia, is inhibited by gelatin or gum, whereas the diuresis produced by sulphates, and due partly to stimulation of renal cells, is not thus inhibited.

Sugars have universally been regarded as typical crystalloids and typical diuretics. If any fact in physiology seems established beyond question, this one seems so. Nobody refers to it in any but axiomatic fashion. The diuretic action of sugars has been thus axiomatically used to explain the polyuria of diabetes. The expressions to this effect are too numerous to recount; but a few may be quoted as examples.

Naunyn (p. 198) names polyuria as the most immediate effect of the sugar excretion. Elsewhere he refers to the fact that increased sugar elimination generally means increased diuresis.

Von Noorden [(1), p. 124] says concisely, "Mehr Zucker bringt mehr Harn mit sich." He then expands the statement. Also von Noorden [(3), p. 602] says: "The quantity of water [in the urine] is usually greater the more sugar there is. Sugar is a diuretic. The blood and tissues become depleted, and increased thirst results. The polydipsia is obviously a secondary phenomenon; it almost always disappears when the glycosuria is controlled by dieting." On the same page, he mentions the occasional cases of "diabetes decipiens," in which marked hyperglycemia and glycosuria accompany a normal urine output [see Chapter III; also von Noorden (1), p. 127]. But these are exceptions.

Lepine [(1), pp. 463 and 467] describes diabetes decipiens, but notes that in general, there is correlation between the percentage of sugar and the quantity of urine.

Kleen (p. 77) says: "Hyperglycemia in itself acts on the kidneys as a diuretic. When enormous doses of saccharids are given, the urine always suddenly increases. . . . If the supply of carbohydrates in the food is restricted and hyperglycemia and glycosuria cease, polydipsia and polyuria often also cease." But he adds: "Polyuria may, however, arise also in consequence of direct vasomotor influences, and not be the effect but the cause of increased thirst and polydipsia. Thus, lesion of the 'lobus hydruricus' in the vermis, near the seat for Bernard's puncture, causes diabetes insipidus, as does also lesion of Kahler's centers. Further, the increased excretion of urine is observed in progressive paralysis. These facts suffice to explain, easily, cases of diabetes mellitus with slight glycosuria and marked polyuria, and cases of diabetes insipidus with slight traces of sugar, and the circumstance that the polyuria sometimes remains after the disappearance of the glycosuria in the rare cases of incomplete recovery from diabetes mellitus."

Herter (p. 387) says: "Two other important symptoms of diabetes — polyuria and excessive thirst — are referable to the considerable loss of glucose through the kidneys. If we experimentally increase the sugar-content of the blood in a dog or other animal, there is a prompt increase in the volume of the urine. Some increase in the volume of the urine always attends the excretion of a considerable quantity of sugar, doubtless because the additional supply of fluid is required to enable the epithelial cells of the kidneys to perform the work of separating glucose from the blood. The amount of urine passed by some diabetics amounts to 4000 or 5000 cc. in 24 hours, but in cases where the quantity of sugar in the urine is less than 1 per cent the volume of the urine may not be appreciably increased."

Futcher (p. 771) says: "The increase in the quantity of urine is referable to the hyperglycemia. Owing to the increased quantity of glucose in the blood, the latter becomes hyperisotonic, and the fluids of the tissues are absorbed into the circulation more rapidly than in the normal individual, and consequently more water is secreted by the kidneys. The amount of urine may reach 10 to 20 litres."

The diuretic action of sugar is also invoked for explanation in conditions other than diabetes. It is sometimes made use of to explain the diuresis resulting from phloridzin or adrenalin, as will be observed in the discussion between Loewi (2), Frey, and Biberfeld on this subject.

We pass now to the experimental evidence on which this universal opinion of sugar-diuresis is founded. It is abundant, and the earliest works may be omitted.

Albertoni in 1889 published studies concerning the diuretic, circulatory, and nervous effects of sugars. The later papers (2 and 3) contain criticisms of Hedon (5) and of Hedon and Arrous. The work was all with intravenous injections. There is some dispute as to the part played by osmosis and by vascular changes, but perfect agreement concerning the fact of diuresis.

Hedon and his pupil Arrous also engaged in polemic with Lamy and Mayer (1, 2, 3). The latter found no constant relation between diuresis from sugar and increased arterial pressure or renal vaso-dilatation; also, no constant relation between diuresis and the viscosity of the blood, or the molecular concentration of the blood, or the speed of circulation. But diuresis was found as a rule proportional to the quantity of sugar in the blood

at the given moment. In comparing the diuretic effects of different sugars, Lamy and Mayer quote Richet and Moutard-Martin, who considered all sugars "about equally diuretic," and also the molecular-weight views of Hedon and Arrous. But Lamy and Mayer, on the basis of the water, urea, and salts eliminated, placed sugars in the following descending scale as diuretics: lactose, saccharose, glucose, maltose. They concluded that the diuretic action of sugars varies inversely with the assimilability. (The erroneous idea respecting relative assimilability was pointed out by Arrous.) They called lactose a "true" diuretic, the others "apparent" diuretics. In the debate concerning relative activity of different sugars, they describe an experiment in which dextrose elicited 312 cc. urine, while the same dose of lactose yielded 848 cc. once and 680 cc. another time. All their work was done with dogs weighing about 10 kilos, injected intravenously with 50 g. sugar in 100 cc. water. The animals were chloralized, or curarized with artificial respiration. One kidney was in a plethysmograph, cannulæ were placed in the ureters, tracings were taken from cannulæ in blood-vessels, etc. In one set of experiments, there was absence of diuresis, and even anuria, after injection of lactose or saccharose in the dosage mentioned. Some of these results may be interpreted as due to the highly abnormal conditions.

Arrous (1) and Hedon (6) answered Lamy and Mayer, interpreting the mechanism of diuresis differently. They invariably found dextrose a more powerful diuretic than lactose. Hedon recognizes that the question is complex, but considers molecular weight to be one of the most important factors. He thinks that v. Limbeck's law of relations between the molecular weight and the diuretic action of salts can be proved to hold for sugars; the contrary would be surprising. To show that the percentage of sugar in the blood is not always the decisive factor which Lamy and Mayer consider it, Arrous mentions an experiment in which there was 11 g. of glucose per litre of blood, without polyuria.

Arrous (2) claims to have established a "diuretic coefficient," $\frac{\text{Volume of urine}}{\text{Volume solution injected}}$. Using rabbits, he asserted that:

(*a*) Each sugar has a definite diuretic coefficient for a definite concentration.

(*b*) The coefficient is independent of the size of dose.

(*c*) For the same sugar, the coefficient diminishes with dilution and increases with the concentration of the solution injected. He found that the diuretic activity varies inversely with the molecular weight of sugars, and depends directly upon osmotic tension. In order to meet the experimental conditions of Lamy and Mayer, he tested his results on dogs, and found the same differences between dextrose and lactose as in rabbits. The mean value of the "coefficient" for dextrose was 2.2, for lactose 1.6, for saccharose 1.2. The injections were of 25 per cent solutions, in dosage of 5 g. sugar per kilo, at a rate of 20 cc. per minute. Urine was collected for $1\frac{1}{2}$ hours. After this time, the urine is said to have returned to normal. Arrous (3) recognizes a physical and a chemical cause for the diuresis. The former governs almost entirely the earlier part of the process, and produces a greater elimination of water; it depends upon the molecular weight and osmotic tension of the respective sugars. The latter is excito-secretory, has little effect at first but is felt more during the later part of the diuresis, and produces a greater elimination of sugar. The circulatory changes and factors governing them are reviewed in detail. Arrous (4) deals chiefly with arguments. The conclusion is that all sugars are diuretics; the difference is only of degree. The distinction between lactose as a "true" diuretic and other sugars as "apparent" diuretics is unfounded. The interesting statement is made that sugars on intravenous injection are superior to any other diuretics; superior, for example, to sodium nitrate.

Though the general results of all these authors are not to be contested, a few critical remarks are in order. The dispute concerning the diuretic efficiency of intravenously injected dextrose and lactose probably rests upon experimental conditions. The general impression now seems to be in favor of lactose. When Hedon considered that sugars should obey the law of salts, and that failure to do so would be surprising, he did not reason as closely as usual. Injected salts circulate till excreted by the kidneys, and meanwhile exert their diuretic effects. If a large proportion of a certain salt were disposed of in some totally different manner, this salt could not be expected to obey the general law. Among sugars, it happens that lactose is excreted like a salt. But dextrose is mostly consumed in the tissues; even with rapid injection, generally less than half appears in the urine. Thus the law is broken. The diuretic coefficient devised by Arrous depends

partly upon a standard rate of injection. The slower the injection, the greater the utilization and the less the diuresis that may be expected. It is conceivable that in very rapid injection, dextrose may be a more active diuretic than lactose; and that in slower injection, the reverse may be true. The widely varying results of the same and different authors, and figures such as cited by Arrous, of 11 g. dextrose per litre of blood without polyuria, indicate that the bottom of the problem is not reached. Renal injury is one factor, but still another must be brought in before the solution is found.

Fleig injected dogs intravenously with isotonic or slightly hypotonic sugar solutions. The injections were very slow, lasting 3 hours, at a constant rate of 0.7 to 1 cc. per minute per kilo of weight. Urine was taken by catheter every 15 minutes during injection, and every 2 hours thereafter. Each specimen was examined as to density, solid residue, freezing point, and quantity of sugar and chlorides. Comparison was made with 0.9 per cent NaCl solution. He found the total diuretic effect of dextrose and lactose about the same; differences between them during injection were balanced by the opposite differences following injection. The total elimination of solids other than sugar is about the same for dextrose and lactose. But the quantity of lactose excreted is 7 or 8 times the quantity of dextrose. Excretion of the latter practically ends with injection; excretion of the former continues 12–24 hours thereafter. Dextrose is therefore preferable, because less of it passes through the kidney. During the 3 hours of injection, the total water eliminated by NaCl solution is slightly less than that by glucose, and only about half that of lactose. During the following 12 hours, NaCl is somewhat superior; but the total liquid diuresis from NaCl is slightly below that from dextrose or lactose. The total elimination of solids (subtracting sugars and chlorides) is a fraction greater from NaCl than from sugars. Since the kidney has less work to do, sugar solutions are concluded to be preferable to NaCl solutions as diuretics.

Sollmann (2) used dextrose as one of a long series of substances for perfusion of the kidney post mortem. The brief record is: "Dextrose. The effect of this solution, when compared with sodium chloride, was small and inconstant. There was generally a trifling diminution in the vein flow and increase in the ureter flow." Starling, in agreement with Heidenhain, classified sugar

as one of those substances which, injected into the blood-stream, acts as a "lymphagogue of the second class." Magnus-Levy [(4), p. 161] notes the increase of urea observed by Forster after intravenous injections of sugar.

All the experiments thus far mentioned have been with intravenous injections. But there is confirmatory evidence by other methods. Thus Kossa observed intense diuresis after his subcutaneous sugar injections, and saw here a similarity with diabetes. But Kossa used chiefly saccharose; and he failed to notice primary oliguria when present.

Nobecourt and Bigart reported that intraperitoneal injections of dextrose in rabbits, in doses sufficient or insufficient for glycosuria, caused increased excretion of urea. Small doses caused no diuresis nor increase of chlorides. Large doses caused diuresis and increased output of chlorides, continuing long after the glycosuria. This last statement is correct; but the authors evidently failed to notice the primary oliguria.

The figures of Fritz Voit in human cases permit no conclusions as to diuresis from the injections. Scott, and Underhill and Closson, found that subcutaneous injections in dogs increase the output of total nitrogen, but they did not follow the different stages of water-diuresis.

A number of authors have noted the effects of sugar in diabetic animals. Von Mering and Minkowski (p. 386) mention an experiment in which the giving of sugar to a depancreatized dog increased the excretion of nitrogen. Minkowski [(1), pp. 20–21] describes experiments with depancreatized dogs, such as the following.

Day after operation	Feeding	Urine		
		Quant. cc.	Dextrose g.	Nitrogen g.
11	300g. meat.	200	12.8	4.88
12	" "	250	14.5	5.45
13	" "	260	15.1	5.46
14	" "	250	16.	5.95
15	" "	200	12.4	4.2
16	" " with 18g. dextrose.	400	30.4	4.44
17	300g. meat.	160	13.9	3.58

The marked increase, not only in quantity of urine but also in sugar, in the 24 hours following the sugar-feeding, is easily seen. Minkowski figured that the *excess* (above protein-sugar)

of sugar excretion in this 24 hours amounted to 18.2 g. (a little more than the amount fed). Similarly, an *excess* of 4.1 g. is reckoned also for the last 24 hours of the experiment.

14-KILO DEPANCREATIZED DOG.

Day after operation.	Feeding.	Urine.		
		Quantity, cubic centimeters.	Dextrose, grams.	Nitrogen, grams.
5	500 g. meat	490	53.4	16.22
6	500 g. meat	610	58.6	19.95
7	500 g. meat+75 g. dextrose	1520	144.4	23.41
8	500 g. meat+75 g. dextrose	920	103.0	14.63
9	500 g. meat	470	49.4	15.51
10	500 g. meat	500	54.0	17.45
11	500 g. meat	660	61.4	21.12

In this experiment, Minkowski figures that of the first 75 g. dextrose fed, 74.2 g. appeared in the urine; and of the second 75 g. dextrose fed, 59.2 g. appeared in the urine. Except for the impaired digestion, the figures for both sugar and nitrogen following the sugar-feedings would be much higher. The fall of nitrogen in each experiment indicates the diminished assimilation of food.

On page 92, Minkowski describes an experiment with subcutaneous injection of dextrose; but as his only interest here was the utilization of sugar, and the injection was 300 cc. 5 per cent dextrose, the diuretic effect of the sugar cannot be judged.

Allard (2) gave subcutaneous injections of dextrose in incompletely and completely depancreatized dogs. The completely depancreatized animal showed an increased excretion of dextrose greater than the quantity injected. The incompletely depancreatized animal excreted less than the amount injected.

All these researches, and many others, support the universal idea that sugar is a diuretic in diabetes and in non-diabetes.* Nevertheless, it is possible to glean from the literature a few observations in disagreement with the others. For introduction may be taken the following quotation from Magnus-Levy [(4), p. 413]. "Owing to the lack of investigations, it is impossible to say whether the glycogen resembles fat in being deposited as a dry waterless mass, or is laid down swollen with water. If the

* This noun has been found convenient to signify all conditions (including non-diabetic forms of glycosuria) other than true diabetes.

latter were the case, the accumulation of glycogen would involve the simultaneous increase of the absolute amount of water in the tissue. It is possible that the retention of water by dogs fed upon bread, which Voit records, may be explained in this way. The fact that when human beings lose carbohydrate they also give up water from their bodies may here be repeated for sake of comparison."

Zuntz (2) interprets his metabolism experiments as indicating that glycogen is deposited swelled with four-fold its weight of water.

Wimmer, who worked with starch-feeding of fasting dogs, says (p. 194): "Die Wasserbilanz zeigt, dass mit Erhöhen der Stärkezufuhr ein H_2O-Ansatz erfolgt, während bei Erniedrigung derselben wiederum Wasserabgabe stattfindet, was offenbar mit der Aenderung im Glykogen- und Zuckergehalt des Körpers zusammenhängt, — ein Befund, das im hiesigen Institute stets bei ähnlichen Versuchen gemacht wird, und dessen auch E. Voit und Zisterer schon Erwähnung getan haben."

Pavy [(1), p. 20 ff.] observed like others the diuresis following large intravenous injections of sugar. Pavy (3) observed changes rapidly occurring in the injected dextrose. Pavy and Godden (2) made the greatest of recent advances in the subject, when they noted that intravenous injections of dextrose in rabbits cause glycosuria if large and given quickly, and no glycosuria if smaller and given slowly. In the latter case, there is marked *diminution* in the output of urine. Glycosuria may be absent even when the blood-sugar is increased to 0.2 per cent. Strong NaCl solution lowers the tolerance. The methods used were correctly chosen for accurate study, inasmuch as the animals were kept upright, comfortable, free from pain or nervousness.

The observations of Burton-Opitz may be considered somewhat analogous; viz., that small doses of concentrated dextrose solutions injected intravenously cause increase of the viscosity and specific gravity of the blood, while large doses cause decrease of both. Zanda (1) observed differences in the viscosity of the blood under different conditions when its sugar-content was increased *in vivo* or *in vitro*, and suggested the formation of combinations as an explanation. The subject deserves further investigation.

McGuigan (3) made slow intravenous injections of very dilute sugar solutions in rabbits. Diuresis was not the object of his study, but his figures show a very small output of urine.

Heilner (1), working with large subcutaneous injections of dextrose in rabbits (about 10 g. per kilo), made the only exact observation that exists in the literature concerning what happens in such cases. Though his injections amounted to 300 cc. of 10 per cent solution, yet he found both the quantity of urine and the output of nitrogen markedly diminished on the day of injection. Then, during one or two days following this first day, the urine became increased.

Heilner (6) reports that subcutaneous injections of saccharose or of NaCl may cause oliguria in rabbits. After injection of strongly hypertonic salt or sugar solution, there is often a diminution of the urine, which is specially striking in view of the greatly increased intake of liquid. But with hypotonic solutions or with distilled water the opposite occurs, viz., a rich diuresis. He considers that the oliguria resulting from concentrated dextrose and saccharose solutions depends on different causes. In the case of dextrose, it concerns a centrally regulated protective mechanism. In the case of saccharose (and salts?) it is due to injury of the renal cells. Protein metabolism in fasting rabbits is markedly diminished by saccharose injection, especially on the day of injection; the mechanism is not a sparing action of sugar, but rather a disturbance of cell metabolism by osmotic processes. On the contrary, fat metabolism is markedly increased. A variety of substances, in solutions that differ from the body-fluids in osmotic pressure, are able to produce these effects upon both protein and fat metabolism. Heilner's results concerning diuresis are to be explained partly by the easy vulnerability of the rabbit's kidney.

Halasz (3), in a paper devoted chiefly to sugar enemas, made incidental observations which are worth quoting verbatim.

"Ich möchte gerne die Aufmerksamkeit der Autoren auf eine interessante und von mir schon anlässlich früherer Tierversuche bemerkte Erscheinung lenken, welche sich darin äussert, dass zwischen den quantitativen Schwankungen in der Zuckerresorption und denen im Quantum des täglich entleerten Urins ein gewisser Zusammenhang bestehe. Vor Jahren [1902] verabreichte ich im Institute des Herrn Prof. v. Klug kaum 6–7 kg. wiegenden kleinen Hunden je 100–180 g. Dextrose, um bei ihnen alimentäre Glykosurie hervorzurufen, und bei dieser Gelegenheit fiel mir auf, dass am Tage des Versuches die Tiere im Vergleich zu den früheren Tagen weniger Urin entleerten — der Unterschied betrug 25–40 % — worauf sodann in den nächstfolgenden Tagen Polyurie auftrat. Diese Erscheinung konnte ich mir nur schwer erklären: G. Sée, Mayard, Dujardin-Beaumetz schreiben dem Zucker diuretische Wirkung zu, und Kossa fand bei seinen neueren Versuchen ebenfalls, dass nach grösseren Zuckerquantitäten Polyurie auftrete, was er so erklärte, dass sich infolge

der Einwirkung des Zuckers die Blutgefässe der Nieren erweitern, dass der Blutdruck stärker werde und dass der Zucker einen direkten Reiz auf das Nierenepithel ausübe.

"Bei dieser Gelegenheit möchte ich nur erwähnen, dass ich die oben erwähnte Erscheinung auch damals konstatierte, als ich meine Versuche an Menschen machte. Und, obzwar bei Applikation von Zuckerklysmen die Schwankungen zwischen eingeführtem Zuckerquantum und Urinquantum nicht so gleichmässig erscheinen, als wenn man den Zucker per os oder noch eher, wenn man ihn subkutan gibt, indem man *doch die mit dem Stuhle entleerte Wassermenge ebenfalls in Rechnung ziehen muss*, so tritt es z. B. im Falle der Versuchsperson J. T. sehr deutlich zutage, dass bei diesem Individuum, bei welchem im Stuhlquantum verhältnismässig geringere Schwankungen auftraten, das Urinquantum starken Schwankungen ausgesetzt war, indem es gewöhnlich 1500 ccm., nach 50 g. Dextrose 1580 ccm., nach 148.0 g. Traubenzucker 920 ccm. und schliesslich nach 195.2 g. auf 680 ccm. sank. In anderen Fällen in denen die Zuckerresorption minimal war, zeigte auch das tägliche Urinquantum keine besonderen Schwankungen, obgleich z. B. bei dem, im 4. und 11. Versuche figurierenden Individuum [J. L.] das tägliche Urinquantum 1400–1500 ccm., nach 50.0 g. Traubenzucker 1700 ccm. beträgt und nach 98 g. Dextrose auf 850 ccm. sinkt.

"Ich bin weit entfernt davon, auf Grund weniger Fälle eine Regel aufstellen zu wollen, muss es aber demnach für beachtenswert halten, dass Urinquantum in gewissen Fällen nach Einführung grösserer Zuckermengen auffallend sinke, und werde ich gelegentlich auf diese Tatsache noch hinweisen."

Particularly interesting in this connection are certain recent publications from Lusk's laboratory [see Lusk (3) and Fisher and Wishart]. Here it is shown that after feeding dextrose, the blood-sugar is increased, and respiration and calorimetry experiments indicate an increased combustion of dextrose. During this time, hemoglobin tests and corpuscle counts of the blood demonstrated a hydremic plethora, and simultaneously both the quantity and the nitrogen of the urine were diminished. When the excess of sugar was completely disposed of, there was a marked sudden polyuria, with a return of the blood to normal. These findings give a gratifying support to the conclusions at which I have arrived in this chapter.

Synopsis.

The suggestions concerning the combined state of dextrose in non-diabetes and its free state in diabetes were reviewed at the outset. *If such a difference exists, it should be demonstrable by some physiological test.* Such a test seems to be found in the diuretic properties of dextrose. The following are the laws observed.

(A) In diabetes, dextrose is a diuretic however given, whether intravenously, orally, subcutaneously, intraperitoneally, or by any other way.

(B) In non-diabetes, dextrose is a diuretic when given intravenously (unless the dose is sufficiently small to permit prompt combination, in which case, as Pavy proved, the urine is diminished). Dextrose is an anti-diuretic — that is, it diminishes markedly the output of urine — when given orally, subcutaneously, intraperitoneally, or in any way except intravenously. Dosage and all other factors are entirely immaterial. The oliguria during glycosuria is followed by polyuria after cessation of glycosuria.

By reference to the laws of diuretic action of colloids and crystalloids, it is evident that sugar in diabetes behaves as a typical crystalloid. In non-diabetes, sugar injected intravenously behaves as a typical crystalloid, but introduced by any other channel behaves as a typical colloid.

Experiments.

The mass of experiments on the question are hard to arrange in orderly manner. Classification might be called for on the basis of different species of animals, different individual animals, different sugars, different concentrations, different channels of administration, administration during fasting and during feeding, etc. But nothing elaborate is demanded. The fact is very simple, viz., that sugars in normal animals are diuretics when given intravenously (aside from Pavy's important discovery), and anti-diuretics when given otherwise. Therefore, though tests have been made in many different directions, the animals will merely be set down here in their individual order, and the reader permitted to draw his general conclusions from each.

As it was impossible to follow the excretion of all urinary constituents, water and nitrogen were chosen as the important ones for the present purpose. The nitrogen-determinations were made not in all, but in a sufficient number. Dilute sugar solutions of course require saline control; others are controlled by the normal output. Experiments have been made with drinking-water supplied ad libitum, and with fixed quantities given by tube, and with other variations. The material will be presented according to the following classification:

A. Experiments with non-diabetic animals.
B. Experiments with diabetic animals.
C. Interpretation of experiments.

A. Experiments with Non-diabetic Animals.

Most of the earlier orientation-experiments will be omitted; one, in a guinea-pig, may be presented to exemplify the behavior of this species.

Guinea-pig 44; male; adult.

In metabolism cage, under constant conditions of diet and surroundings, from May 10 till after close of experiment. Urine in 24 hour specimens collected each morning.

Date	Weight g.	Urine						Treatment
		Quant. cc.	Appear.	React.	Sp.G.	Benedict	Alb.	
May 24	685							Subcut. injection of 140cc. 10% Kahlbaum dextrose solution scattered over whole body (a trifle over 20g. per kilo.) Acts somewhat unwell. Eats little or nothing.
" 25	720	90	Clear, almost water-pale.	Faintly alk.	1018	Very Heavy	Neg.	
" 26	635	85	Yellow, turbid.	Alk.	1020	Neg.	"	
" 27	620	15	Dark, turbid.	"		"	"	
" 28	630	45	Dark, turbid.	"		"	"	Acts entirely well.
" 29	665	43	Dark, turbid.	"		"	"	
" 30	665	40	Dark, turbid.	"	1025	"	"	Subcut. injection of 140cc. 0.85% NaCl solution scattered over whole body. Shows the usual depression and diminished appetite.
" 31	625	133	Normal brown. Slightly turbid.	"	1018	"	"	
June 1	600	10	Dark, turbid.	"		"	"	
" 2	630	22	Dark, turbid.	"		"	"	

Summary for Pig 44.

Ten per cent dextrose solution in dosage of over 20 g. per kilo causes intense glycosuria, but less diuresis than the same quantity of plain saline. The increase on the second day after dextrose as compared with the second day after saline is evident. The increased weight (due to water retention) on the day after dextrose may be compared with the decreased weight after saline.

Rabbit 32; male; weight 2 kilos.

The experiments consist in comparisons between a series of fast-days, instituted to aid in ruling out differences due to impaired appetite. Water was supplied at frequent intervals, and

measured. Catheterization at hours stated. The animal was constantly in the same cage, and all conditions were uniform during and between experiments. The results may be tabulated as follows.

Date	Hour	*Treatment	Water cc.	Urine cc.	Sugar in Urine
Apr. 16	5 P.M.	24 hours starvation.	20	8	0
" 17	10.30 A.M.		25	30	0
" 28	5 P.M.	24 hours starvation; subcut. injection of 24cc. 50% lactose solution.	45	35	Very heavy
" 29	10.30 A.M.		25	32	Mod. to heavy
May 7	5 P.M.	24 hours starvation; subcut. injection of 15cc. 80% dextrose right side.	55	6	0
" 8	10.30 A.M.		60	26	0
" 16	5 P.M.	24 hours starvation; subcut. injection of 15cc. 80% dextrose left side, 15cc. 10% NaCl right side.	130	14	9.73%
" 17	10.30 A.M.		45	10	1.46%
" 21	5 P.M.	24 hours starvation; subcut. injection of 15cc. 10% NaCl left side.	75	65	0
" 22	10.30 A.M.		55	54	0
" 31	5 P.M.	24 hours starvation.	40	32	0
June 1	10.30 A.M.		20	60	0

*Each starvation period began at 10.30 A.M. The quantities of water and urine on the day following are for the 5 P.M.-10.30 A.M. period.

Summary for Rabbit 32.

April 16 was a control fast-day. May 31 was another.

April 28 was a fast-day, with subcutaneous injection of 12 g. lactose. The result was an output of urine intermediate between that of April 16 and that of May 31.

May 7 was a fast-day, with subcutaneous injection of 12 g. dextrose. There was no glycosuria nor albuminuria. The excretion of urine was less than on April 16 or May 31, and the ingestion of water was greater.

May 16 was a fast-day, with simultaneous subcutaneous injection of 12 g. Kahlbaum dextrose and 15 cc. 10 per cent NaCl solution. The result was increased drinking and diminished urine.

May 21 was a fast-day, with subcutaneous injection of 15 cc. 10 per cent NaCl solution. The result was increased drinking and marked diuresis. Diminution of urine as witnessed by Heilner was not found with this dosage.

The conclusions are:

(1) Lactose given subcutaneously in a normal animal may exhibit no diuretic action beyond that due to increased drinking.

(2) The normal effect of subcutaneously injected NaCl is diuresis. Other results should be considered as exceptions.

(3) Dextrose given subcutaneously in a normal animal is an anti-diuretic, diminishing the quantity of urine when given alone, and neutralizing the effect of NaCl, a typical diuretic. The fact that the oliguria of May 16 accompanied a glycosuria of 9.73 per cent should be duly noted.

Rabbit 50; male; weight 2400 g.

Fast-days were instituted, as in Rabbit 32. Diet and all other conditions between-times were constant. The results may be tabulated as follows.

Date	Hour	*Treatment	Water cc.	Urine cc.	Sugar in Urine
May 11	5 P.M.	24 hours starvation.	80	35	0
" 12	10.30 A.M.		55	80	0
" 15	5 P.M.	24 hours starvation. Subcut.injection of 25cc. 50% Merck dextrose.	70	30	1.2%
" 16	10.30 A.M.		0	10	0
" 18	5 P.M.	24 hours starvation. Subcut.injection of 15cc. 80% dextrose.	113	7	0.42%
" 19	10.30 A.M.		20	20	0.52%
" 21	5 P.M.	24 hours starvation. Subcut.injection of 15cc. 10% NaCl.	155	87	0
" 22	10.30 A.M.		80	75	0
" 31	5 P.M.	24 hours starvation.	48	31	0
June 1	10.30 A.M.		38	75	0

*Each starvation period began at 10.30 A.M. The quantities of urine and water on the day following are for the 5 P.M.-10.30 A.M. period.

Summary for Rabbit 50.

May 11 was used as a control fast-day. May 31 was another.

May 15 was a fast-day, with subcutaneous injection of 5 g. dextrose per kilo. The urine was diminished, in spite of glycosuria of 1.2 per cent.

The same experiment was repeated on May 18, and the urine was more markedly diminished. The difference in the concentration of the solutions may have been a factor.

May 21 was a fast-day, with subcutaneous injection of 15 cc. 10 per cent NaCl solution. The result was the typical diuresis.

Dog 17.

The animal fasted November 26 to December 17. The following is an excerpt from the protocol.

DOG 17.

Date	Weight g.	Temp.	Treatment	Water	Urine		
					Quant. cc.	Benedict	Nitro.
Dec. 11	6600			7	9 A.M. 65	-	1.98
" 12	6410	9 A.M. 100^8		5	9 A.M. 34	-	1.65
" 13	6300	9 A.M. 100^4		25	9 A.M. 24	-	1.41
" 14	6150	9 A.M. 100^2 5 P.M. 102	At 1 P.M. finished subcut. injection of 61.5g. Merck dextrose in 100% solution. (10g. per kilo.)	Up to 5 P.M. 325	9 A.M. 26 5 P.M. 90	- 0.85% (0.765g.)	1.6
" 15	6450	9 A.M. 101^2 P.M. 101^4		During night 240	9 A.M. 154 Total 24-hr. 244	1.2% (1.85g.)	2.34
" 16	6075	A.M. 101^6 P.M. 101^8		0	9 A.M. 190	-	2.81
" 17	5930	A.M. 101^3		25	9 A.M. 20	-	0.88

Summary.

After subcutaneous injection of 10 g. dextrose per kilo on December 14, the evening urine and that of the following morning

were increased in amount. The anti-diuretic effect was less marked than usual. But it is to be noted that the anti-diuretic effect is present nevertheless. The urine is less than should be expected from the water consumed; water-retention is proved by the *increased weight* of December 15, and the diuresis is greater *after* than *during* glycosuria, *i.e.*, 244 cc. on the evening of December 15 as opposed to 90 cc. on the evening of December 14, and 190 cc. on the morning of December 16 as opposed to 154 cc. on the morning of December 15.

DOG 17.

Diet 400g. Meat.
Water 100cc. by tube at 9.30 A.M. & 5 P.M.

Date	Weight	Treatment	Urine			*Feces	
			Quant. cc.	Benedict	Nitro. g.	g.	Nitro g.
Jan. 18	8695		280	Neg.	12.38	14.	0.42
" 19	8600		425	"	13.34	40.	0.98
" 20	8525	9.30 A.M., subcut. injection of 85.5g. lactose (10g. per kilo) in 50% solution.	330	"	12.46	25	0.65
" 21	8480		440	Heavy	10.16	9.	0.4
" 22	8275		450	Slight	17.61		
" 23	8375		194	Neg.	9.34		
" 24	8285		365	"	12.1		

*Feces weighed and analyzed fresh.

Summary.

With a constant daily intake of food and water at fixed hours, lactose injected subcutaneously in dosage of 10 g. per kilo on January 20 proved itself slightly anti-diuretic. That is, any increase of urine present on January 21 is less than should be accounted for by the water in the 171 cc. injection. Also, the urine of December 22, containing little lactose, is more than the urine of December 21, containing much lactose. Also, though large sugar injections cause increased nitrogen loss, the excretion on December 21 was actually diminished, and the increase did not appear till December 22. Both the urine and the weight prove that the anti-diuretic action of lactose is far less than that of dextrose.

DOG 17.

Diet 400g. Meat. Water ad libitum.

Date	Weight g.	Temp.	Treatment	Urine		
				Quant. cc.	Reducing Sugar	Saccharose
Feb. 23	8750	9 A.M. 102		9 A.M. 440	-	
" 24	9060	9 A.M. 101^6		9 A.M. 325	-	
" 25	9010	9 A.M. 102^2		9 A.M. 320	-	
" 26				9 A.M. 340	-	
" 27	9305	9 A.M. 101^8	At 1 P.M. subcut. injection of 23.5g. Merck saccharose in 50% solution. (2.5g. per kilo). Has eaten well. Drinks much.	9 A.M. 390	-	
		5 P.M. 101^5		5 P.M. 245	0.2%	Heavy
" 28	9350	9 A.M. 101^6		9 A.M. 615	-	Heavy
				5 P.M. 365	-	-

Summary.

With free drinking of unmeasured water, the subcutaneous injection of $2\frac{1}{2}$ g. saccharose per kilo on February 27 caused a greatly increased output of urine. At the same time a retention of water is indicated by the increase of weight and the diuresis on the evening of February 28.

DOG 17.

Diet 225g. Bread-and-Meat Mixture.
Water ad libitum.

Date	Hour	Treatment	Urine	
			Quant. cc.	Sugar
May 2	9.30 A.M.	Subcut. injection of 200cc. 20% dextrose solution.	90	faint
	5 P.M.		32	0.6%
" 3	9.30 A.M.	Subcut. injection of 200cc. 20% commercial glucose solu.	190	faint
	5 P.M.		60	mod.
" 4	9.30 A.M.		330	---
	5 P.M.		80	---
" 5	9.30 A.M.	Subcut. injection of 100cc. 20% Kahlbaum dextrose solu.	360	---
	5 P.M.		18	slight
" 6	9.30 A.M.	Subcut. injection of 100cc. 20% Kahlbaum dextrose solu.	210	---
	5 P.M.		20	0.5%
" 7	9.30 A.M.		260	---
	5 P.M.		40	---
" 8	9.30 A.M.		110	---
	5 P.M.		40	---
" 9	9.30 A.M.	Subcut. injection of 100cc. 10% NaCl solution.	270	---
	5 P.M.		300	---
" 10	9.30 A.M.		410	---
	5 P.M.		150	---

Summary.

Prior to these experiments, the dog had been partially depancreatized, so that the dextrose tolerance was lowered. Notwithstanding the large volume of injection, the evening urine after injection of dextrose was frequently less than on control-days. A strong contrast is presented by the prompt and marked diuresis following the subcutaneous injection of a hypertonic NaCl solution.

Dog 18.

This dog fasted from November 25 to December 25. On December 3, the intravenous injection of 5 cc. 80 per cent saccharose solution had a diuretic effect. An excerpt from the later protocol is as follows.

DOG 18.

Measured Water Constantly in Cage.

Date	Weight g.	Treatment	Water cc.	Urine			
				Quant. cc.	Benedict	Saccharose	Nitro. g.
Dec. 11	6150		17	30	Neg.		1.46
" 12	6020		40	35	"		1.75
" 13	6000		120	55	"		1.8
" 14	5900	1 P.M., subcut. injection of 59cc. 100% Merck saccharose (10g. per kilo).	9 A.M. 10 5 P.M. 395	9 A.M. 38 5 P.M. 15	" Slight	Heavy	1.85
" 15	6285		180	60	Pos.	"	
		Total 24-hour urine 75cc----------					1.22
" 16	5785		0	356	Neg.	Faint	4.1
" 17	5590		10	106	"	Neg.	1.79

December 14, subcutaneous injection of 10 g. saccharose per kilo had an anti-diuretic effect. Drinking was enormously increased, but the quantity of the urine was little changed, and the nitrogen was diminished. The increased weight proved the retention of water. On December 16, after sugar had nearly disappeared from the urine, came diuresis and the usual increase of nitrogen. These results occurred even with drinking ad libitum.

DOG 18.

Diet 275g. Bread-and-meat Mixture, fed at 5 P.M.
Water 300cc. by tube at 9 A.M. and 5 P.M.

Date	Hour	Treatment	Urine		
			Quant. cc.	Sugar %	Nitro. g.
Mar. 14			425	-	
" 15			660	-	
" 16			535	-	
" 17	9 A.M.	Intravenous injection of 70cc. 50% dextrose (4g. per kilo).	550	-	
	10.30 A.M.		330	3.8	
	12 M.		25	1.6	
	1 P.M.		15	0.2	
	2 P.M.		20	faint	
	8 P.M.		73	-	
" 18			140 (Total 24 hours 603)	-	
" 19			610	-	
" 20			640	-	
" 21			580	-	
" 22			600	-	
" 23			655	-	
" 24			650	-	
" 25			620	-	
" 26					
" 27	5 P.M.		100	-	1.09
" 28	9 A.M.		340	-	4.73
	5 P.M.		90	-	1.
" 29	9 A.M.	Intravenous injection of 70cc. 25% dextrose (2g. per kilo).	360 (Total 24 hours 450)	-	4.33
	1.15 P.M.		350	0.6	
	5 P.M.		64	very faint	2.05*
" 30	9 A.M.		200 (Total 24 hours 614)	-	2.85
	1 P.M.		260	-	
	5 P.M.		30	-	1.71
" 31	9 A.M.		360 (Total 24 hours 650)	-	3.43
	11 A.M.		260	-	
	12 M.		16	-	
	1 P.M.		8	-	
	5 P.M.		29	-	1.4

*Evening nitrogen in each case represents total of urine since 9 A.M.

DOG 18 (Continued).

Date	Hour	Treatment	Urine		
			Quant. cc.	Sugar %	Nitro. g.
Apr. 1	9 A.M.	Intravenous injection of 16.7cc. 25% dextrose (1/2g. per kilo).	320 (Total 24 hours 632)	-	4.16
	11 A.M.		285	0.84	
	12 M.		18	-	
	1 P.M.		18	-	
	5 P.M.		30	-	1.45
" 2	9 A.M.		267 (Total 24 hours 618)	-	3.89
	1 P.M.		280	-	
	5 P.M.		38	-	1.47
" 3	9 A.M.		350 (Total 24 hours 668)	-	4.15
	1 P.M.		230	-	
	5 P.M.		30	-	1.46
" 4	9 A.M.		260 (Total 24 hours 520)	-	4.

Summary.

March 17, the quick intravenous injection of over 4 g. dextrose per kilo caused prompt diuresis, with a subsequent diminution of urine (as authors have noted heretofore), so that the 24-hour total is not above normal.

Remarks. — (1) The sudden osmotic injury from a large intravenous injection, causing albuminuria, does not prevent diuresis when sugar is given in this manner. Renal injury as the cause of the diminished urine after subcutaneous sugar injections thus becomes less probable.

(2) The polyuria ceases long before the glycosuria. One reason probably is that the sugar in the blood has become combined. In spite of the large sudden injection, the total dextrose excreted was far less than half that injected.

March 29, intravenous injection of half the dose (2 g. per kilo) in longer time (5 minutes) caused no albuminuria, but diuresis was well-marked. Nitrogen was increased in the evening urine, but partly compensated in the next morning's specimen, so that the net result for the 24 hours was not an increase.

April 1, the intravenous injection of ½ g. dextrose per kilo caused a slight increase in the evening's total, but no increase of its nitrogen.

Dog 18.

July 31, 24 hours starvation. Drank 75 cc. water during day, 140 cc. during night. Urine-record:

July 31, 5 p.m., 165 cc.
August 1, 10 a.m., 100 cc.

August 5, 24 hours starvation. At 10:15 a.m., 130.5 g. dextrose given by stomach-tube (15 g. per kilo). Drank 250 cc. water during day, 40 cc. during night. Urine-record:

August 5, 11:45 a.m., 25 cc., sugar 1.7 per cent.
2:30 p.m., 21 cc., sugar 2.1 per cent.
5 p.m., 100 cc., sugar faint.
146 cc. = total up to 5 p.m.
August 6, 10 a.m., 115 cc., sugar-free.

Summary.

Comparison is made of two fast-days, on one of which 15 g. dextrose per kilo was given by stomach-tube. In spite of the water given with the sugar, and the increased drinking, the output of urine was less on the sugar-day than on the control day. The loss of weight was correspondingly less on the sugar-day. Diarrhea was so slight as to be negligible.

The specimens containing the most dextrose were the smallest.

Dextrose by mouth is an anti-diuretic.

DOG 60 B, female; mongrel collie; age one year; medium flesh.

Date	Weight g.	Urine Quant.	Sp.G	Benedict	Treatment
June 6	8470				Catheterized 9.30 A.M. and given 254cc. 50% commercial glucose solution by stomach tube. (15g. per kilo). Watched to prevent vomiting. Diarrhea. Water constantly in cage.
11.30 A.M.		43cc.	1040	4.5%	
2.30 P.M.		40cc.	1022	Heavy	
4.30 P.M.		35cc.	1020	Faint	Catheterized at hours stated.
June 7	8030	Specimen		Neg.	Catheterized at 9.30 A.M.

Summary for Dog 60B.

The dose given was commercial glucose, and the experiment merely shows the absence of polyuria during the glycosuria.

Dog 38.

June 6, the dog received 173 cc. 50 per cent glucose solution by stomach-tube (15 g. per kilo), at 9:30 a.m. Urine-record:

11:30 a.m., urine 23 cc., sugar 7.3 per cent.
2:15 p.m., urine 20 cc., sugar heavy.
4:30 p.m., urine 75 cc., sugar faint.

Here the oliguria, especially during the period of heaviest glycosuria, is obvious. It is more striking by reason of the fact that (though record of drinking was not kept) the dog was drinking enormously.

June 14, at 1 p.m., the dog received a subcutaneous injection of 70 cc. 80 per cent dextrose solution (10 g. per kilo). Drinking was heavy as usual. Urine-record:

June 14, 4:30 p.m., urine 20 cc., sugar 0.45 per cent.
June 15, 9 a.m., urine 60 cc., sugar faint.

Here the percentage in the urine was low; there was oliguria as usual.

DOG 19. Weight 8310g.

Starvation from Nov. 27 to Dec.17.
Water ad libitum.

Date	Hour	Treatment	Water	Urine		
				Quant. cc.	Sugar	Nitrogen g.
Dec. 3	9.15 A.M.		25	75	-	1.54
" 4	9.15 A.M.		22	50	-	1.26
" 5	9.15 A.M.	Subcut. injection of 500cc.10% dextrose solu.	55	60	-	1.65
	2-3 P.M.		140			
	5 P.M.			32	4%	
" 6	9.15 A.M.		0	176 (Total 24 hours 208)	0.25%	
	5 P.M.			180	-	2.06
" 7	9.15 A.M.		0	142 (Total 24 hours 322)	-	3.39
" 8	9.15 A.M.		0	55	-	2.18
" 9	9.15 A.M.	Subcut. injection of 500cc.0.85% NaCl solu.	15	56	-	2.23
	5 P.M.			46	-	
" 10	9.15 A.M.		73	210 (Total 24 hours 256)	-	2.68
" 11	9.15 A.M.		0	240	-	1.77
" 12	9.15 A.M.		0	120	-	2
" 13	9.15 A.M.		0	56	-	2.11
" 14	9.15 A.M.	Subcut. injection of 500cc.distilled water.	0	44	-	2.22
	5 P.M.			35	-	
" 15	9.15 A.M.		25	150 (Total 24 hours 185)	-	3.75
" 16	9.15 A.M.		95	154	-	4.24
" 17	9.15 A.M.		20	114	-	4.71

Summary for Dog 19.

The record shows notably smaller output of urine after subcutaneous injection of dextrose solution on December 5, than after a similar injection of saline solution on December 9. After injection of distilled water on December 14, the evening urine was slightly greater, and next morning's urine slightly less, than after the dextrose injection. The slight delay of excretion of the distilled water may be attributed to the pronounced renal injury, as shown by albuminuria. The dextrose caused not a trace of albuminuria.

Dog 21 [see protocol in Appendix].

The dog fasted December 18 to January 2. The results may be summarized briefly as follows.

December 20, a small subcutaneous injection of dextrose (3 g. per kilo) caused a slight glycosuria. Allowing for the water injected and the increased drinking, there was an anti-diuretic effect.

December 27, injection of 3 g. dextrose per kilo intravenously caused no distinct diuresis, possibly because of damage to the kidney of a fasting animal by the rapid injection of a concentrated solution.

December 30, subcutaneous injection of 7 g. dextrose per kilo caused slight glycosuria and well-marked oliguria. On the morning of January 1 came the secondary polyuria.

January 1, feeding of $3\frac{1}{2}$ g. dextrose per kilo produced no glycosuria and no distinct effect upon the volume of urine.

Dog 21 [see protocol].

In this experiment, the dog was on a regular diet of 250 g. bread-and-meat mixture, and receiving water entirely by stomach-tube, viz., 100 cc. at 9:30 a.m. and the same at 4:30 p.m. A summary of the results is as follows.

February 14, intravenous injection of 2 g. dextrose per kilo caused no polyuria. Especially the noon urine, which contained 2.9 per cent dextrose, was diminished as compared with the preceding day. Such results are met with occasionally, but are

exceptional under these conditions. Oliguria such as Pavy reported comes ordinarily from smaller doses or slower injections.

February 17, 10 g. dextrose per kilo by mouth caused marked oliguria. The specimen which contained 1 per cent dextrose was the smallest in bulk. The feces were non-reducing. This diarrhea and oliguria when sugar is taken by mouth are the opposite of the constipation and polyuria which Tuteur witnessed when NaCl, a typical diuretic, is taken by mouth.

Dog 21 [see protocol].

In this experiment, the dog was on a regular diet of bread-and-meat mixture, and received water entirely by tube, viz., 100 cc. at 9:30 a.m. and 100 cc. at 4:30 p.m. A summary of the results is as follows.

March 16, intravenous injection of 4 g. dextrose per kilo was given, in such manner as to test the additional influences of cold, worry, and pain. The resulting diuresis followed the same laws as when these special disturbances are avoided, except that glycosuria continued longer. By noon, the polyuria had ceased, yet the urine still contained in the neighborhood of 5 per cent dextrose, and the blood-test showed hyperglycemia to the extent of 0.396 per cent. The loss of water up to noon (viz., 161 cc.), when the dog had received 100 cc. by tube just after the morning catheterization, is inadequate to explain the failure of diuresis after noon. A diabetic dog with such a percentage of sugar in blood and urine shows persistent diuresis. In today's experiment, the course of events was theoretically as follows.

Just after the injection, the free sugar circulating in the blood caused diuresis. Just as in the diabetic animal, the kidney diluted the sugar as much as possible; hence the percentage in the urine was relatively low. Later, the sugar in the blood became more and more firmly combined, showed more or less colloid behavior, and the quantity of urine thus diminished, while the percentage of urinary sugar increased.

DOG 21.

Diet 225g. Bread-and-meat Mixture.
Water 200cc. by tube 9.30 A.M. and 4.30 P.M.

Date	Hour	Treatment	Urine		
			Quant. cc.	Sugar	Nitrogen g.
Apr. 5	9.30 A.M.		350	-	3.14
	4.30 P.M.		230	-	0.68
" 6	9.30 A.M.		330	-	3.82
	4.30 P.M.		270	-	0.91
" 7	9.30 A.M.	Subcut. injection of 13.2cc. 50% dextrose (1g. per kilo).	270	-	3.5
	1 P.M.		170	-	
	4.30 P.M.		35	-	0.83*
" 8	9.30 A.M.		345	-	3.89
	4.30 P.M.		240	-	0.86
" 9	9.30 A.M.		580	-	3.29
	4.30 P.M.		220	-	0.69
" 10	9.30 A.M.	Subcut. injection of 26.12cc. 50% dextrose (2g. per kilo).	330	-	3.47
	4.30 P.M.		180	faint	0.73
" 11	9.30 A.M.		180	-	3.61
	1 P.M.		248	-	
	4.30 P.M.		65	-	0.98
" 12	9.30 A.M.		425	-	3.97
	1 P.M.		180	-	
	4.30 P.M.		30	-	0.61
" 13	9.30 A.M.	Subcut. injection of 25.7cc. 50% dextrose (2g. per kilo).	330	-	3.41
	1 P.M.		70	-	
	4.30 P.M.		30	-	0.66
" 14	9.30 A.M.		230	-	3.52
	1 P.M.		210	-	
	4.30 P.M.		50	-	0.84
" 15	9.30 A.M.		280	-	3.25
	1 P.M.		220	-	
	4.30 P.M.		15	-	0.64
" 16	9.30 A.M.		260	-	3.38
	1 P.M.		225	-	
	4.30 P.M.		50	-	0.54
" 17	9.30 A.M.	Subcut. injection of 26cc. 80% dextrose (3g. per kilo).	260	-	3.34
	1 P.M.		165	-	
	4.30 P.M.		10	faint	0.47
" 18	9.30 A.M.		360	-	4.39
	1 P.M.		190	-	
	4.30 P.M.		55	-	0.43
" 19	9.30 A.M.		450	-	3.94
	4.30 P.M.		220	-	0.77

*Afternoon Nitrogen always represents total for urine after 9.30 A.M.

DOG 21 (Continued).

Date	Hour	Treatment	Urine		
			Quant. cc.	Sugar %	Nitrogen g.
Apr. 20	9.30 A.M.	Subcut. injection of 33cc. 80% dextrose (4g. per kilo).	290	-	3.39
	1 P.M.		100	-	
	4.30 P.M.		20	-	0.6
" 21	9.30 A.M.		275	-	5.08
	4.30 P.M.		330	-	0.96
" 22	9.30 A.M.		400	-	3.88
	1 P.M.		200	-	
	4.30 P.M.		40	-	0.89
" 23	9.30 A.M.		362	-	4.37
	4.30 P.M.		230	-	0.8
" 24	9.30 A.M.		320	-	4.0
	4.30 P.M.		230	-	0.88
" 25	9.30 A.M.	Subcut. injection of 40.6cc. 80% dextrose (5g. per kilo).	275	-	3.98
	4.30 P.M.		95	very faint	0.53
" 26	9.30 A.M.		280	-	4.54
	4.30 P.M.		350	-	1.59
" 27	9.30 A.M.		420	-	2.71
	4.30 P.M.		260	-	0.77
" 28	9.30 A.M.		260	-	3.3
	4.30 P.M.		194	-	0.76
" 29	9.30 A.M.		170	-	3.46
	4.30 P.M.		170	-	1.
" 30	9.30 A.M.	Subcut. injection of 13.66cc. 50% levulose solution (1g.per kilo).	230	-	3.985
	4.30 P.M.		147	0.43	1.05
May 1	9.30 A.M.		220	-	3.12
	4.30 P.M.		265	-	1.19
" 2	9.30 A.M.		225	-	3.08
	4.30 P.M.		185	-	0.79
" 3	9.30 A.M.	Subcut. injection of 13.6g. levulose (2g. per kilo).	330	-	3.48
	4.30 P.M.		170	0.36	0.75
" 4	9.30 A.M.		290	-	3.5
	4.30 P.M.		240	-	0.7
" 5	9.30 A.M.		330	-	3.78
	4.30 P.M.		180	-	0.72
" 6	9.30 A.M.		340	-	3.47
	4.30 P.M.		180	-	0.708
" 7	9.30 A.M.	Subcut. injection of 20.22g. levulose (3g. per kilo).	415	-	3.76
	1 P.M.		104	0.45	
	4.30 P.M.		20	1.95	0.77

DOG 21 (Continued).

Date	Hour	Treatment	Urine		
			Quant. cc.	Sugar %	Nitrogen g.
May 8	9.30 A.M.		250	-	4.19
	4.30 P.M.		300	-	1.11
" 9	9.30 A.M.		330	-	3.37
	4.30 P.M.		180	-	0.71
" 10	9.30 A.M.	Subcut. injection of 27.58g. levulose (4g. per kilo).	220	-	3.13
	1 P.M.		140	0.62	
	4.30 P.M.		22	4.96	1.17
" 11	9.30 A.M.		160	faint	4.66
	1 P.M.		140	-	
	4.30 P.M.		40	-	1.67
" 12	9.30 A.M.		290	-	5.16
	4.30 P.M.		210	-	0.88
" 13	9.30 A.M.		245	-	3.7
	1 P.M.		160	-	
" 16	4.30 P.M.		210	-	0.735
" 17	9.30 A.M.		400	-	3.91
	4.30 P.M.		220	-	1.01
" 18	9.30 A.M.		335	-	3.84
	4.30 P.M.		210	-	0.61
" 19	9.30 A.M.		320	-	3.8
	1 P.M.		170	-	
	4.30 P.M.		60	-	1.18
" 20	9.30 A.M.	Subcut. injection of 34.4g. levulose (5g. per kilo).	275	-	4.51
	1 P.M.		80	1.59	
	4.30 P.M.		9	5.2	0.445
" 21	9.30 A.M.		290	0.28	5.89
	1 P.M.		275	-	
	4.30 P.M.		70	-	1.13
" 22	9.30 A.M.		360	-	4.185
	4.30 P.M.		230	-	1.12
" 23	9.30 A.M.		290	-	3.625
	4.30 P.M.		280	-	1.15
" 24	9.30 A.M.	Subcut. injection of 7g. galactose (1g.per kilo).	280	-	3.76
	1 P.M.		200	0.65	
	4.30 P.M.		25	0.24	0.895
" 25	9.30 A.M.		270	-	3.65
	4.30 P.M.		280	-	0.91
" 26	9.30 A.M.		350	-	4.44
	1 P.M.		190	-	
	4.30 P.M.		30	-	0.68
" 27	9.30 A.M.	Subcut.injection of 21g. galactose (3g. per kilo).	360	-	4.2
	1 P.M.		185	1.2	
	4.30 P.M.		20	7.3	0.81

DOG 21 (Continued).

Date	Hour	Treatment	Urine		
			Quant. cc.	Sugar %	Nitrogen g.
May 28	9.30 A.M.		205	Slight	4.27
	4.30 P.M.		252	-	0.88
" 29	9.30 A.M.		405	-	4.14
	4.30 P.M.		190	-	0.84
" 30	9.30 A.M.	Subcut.injection of 7g. lactose (1g. per kilo).	265	-	4.05
	1 P.M.		195	2.4	
	4.30 P.M.		33	5.8	1.21
" 31	9.30 A.M.		270	Slight	3.87
	1 P.M.		260	-	
	4.30 P.M.		63	-	1.45
June 1	9.30 A.M.		310	-	4.44
	1 P.M.		190	-	
	4.30 P.M.		40	-	1.265
" 2	9.30 A.M.		310	-	3.865
	1 P.M.		155	-	
	4.30 P.M.		30	-	0.78
" 3	9.30 A.M.	Subcut. injection of 20.73g. lactose (3g. per kilo).	350	-	4.27
	1 P.M.		200	4.29	
	4.30 P.M.		57	14.	1.14
" 4	9.30 A.M.		175	1.6	4.155
	1 P.M.		240	-	
	4.30 P.M.		75	-	1.03
" 5	9.30 A.M.		295	-	3.4
	1 P.M.		200	-	
	4.30 P.M.		18	-	0.75
" 6	9.30 A.M.		320	-	4.31
	1 P.M.		210	-	
	4.30 P.M.		30	-	0.82
" 7	9.30 A.M.	Subcut.injection of 35g. lactose (5g. per kilo).	365	-	4.59
	1 P.M.		240	8.16	
	4.30 P.M.		27	18.34	1.15
" 8	9.30 A.M.		325	2.5	4.87
	1 P.M.		270	slight	
	4.30 P.M.		70	faint	0.88
" 9	9.30 A.M.		300	-	3.64
	1 P.M.		210	-	
	4.30 P.M.		17	-	0.98
" 10	9.30 A.M.		265	-	3.85
	1 P.M.		180	-	
	4.30 P.M.		40	-	1.19
" 11	9.30 A.M.		230	-	3.75
	4.30 P.M.		275	-	0.957
" 12	9.30 A.M.		345	-	3.855
	1 P.M.		235	-	
	4.30 P.M.		20	-	0.92

DOG 21 (Continued).

Date	Hour	Treatment	Urine		
			Quant. cc.	Sugar %	Nitrogen g.
June 13	9.30 A.M.	Subcut. injection of 500cc. 0.85% NaCl Solu.	290	-	3.8
	1 P.M.		310	-	
	2 P.M.		55	-	
	4.30 P.M.		125	-	1.65
" 14	9.30 A.M.		560	-	3.8
	1 P.M.		230	-	
	4.30 P.M.		40	-	0.8
" 15	9.30 A.M.		380	-	4.25
	1 P.M.		210	-	
	4.30 P.M.		30	-	0.82
" 16	9.30 A.M.		280	-	3.53
" 20	9.30 A.M.		360	-	
	4.30 P.M.		205	-	
" 21	9.30 A.M.		290	-	
	1 P.M.		260	-	
	4.30 P.M.		18	-	
" 22	9.30 A.M.	Subcut. injection of 500cc. 5% dextrose solution.	230	-	
	1 P.M.		135	faint	
	4.30 P.M.		140	"	
" 23	9.30 A.M.		650	-	
	1 P.M.		260	-	
	4.30 P.M.		70	-	
" 24	9.30 A.M.		330	-	
	1 P.M.		225	-	
	4.30 P.M.		35	-	
" 25	9.30 A.M.		285	-	
	4.30 P.M.		205	-	
" 26	9.30 A.M.		300	-	
	4.30 P.M.		250	-	
					Saccharose %
" 27	9.30 A.M.	100cc. 25% saccharose solution injected intravenously.	300	-	
	11 A.M.		150	0.48	9.3
	12 M.		90	0.53	6.76
	1 P.M.		50	0.34	2.67
	2 P.M.		52	0.21	0.65
	3 P.M.		35	0.1	0.32
	4.30 P.M.		20	-	-
" 28	9.30 A.M.		210	-	
	1 P.M.		205	-	
	4.30 P.M.		65	-	
" 29	9.30 A.M.		300	-	
	1 P.M.		165	-	
	4.30 P.M.		25	-	
" 30	9.30 A.M.		270	-	
	4.30 P.M.		210	-	

Summary.

April 7, subcutaneous injection of 1 g. dextrose per kilo caused a slight diminution of the evening urine, with corresponding increase the next morning.

April 10, subcutaneous injection of 2 g. dextrose per kilo caused diminution of urine for 24 hours, followed by polyuria in the specimens between noon April 11 and morning April 12.

April 13, another subcutaneous injection of 2 g. dextrose per kilo caused still more marked diminution of the evening urine, and a subsequent compensatory polyuria which seems to be distributed over the several days following.

April 17, subcutaneous injection of 3 g. dextrose per kilo caused diminution of the evening urine, with secondary diuresis beginning the next morning.

April 20, subcutaneous injection of 4 g. dextrose per kilo caused the usual diminution of the evening urine, followed by pronounced polyuria the two succeeding days.

April 25, subcutaneous injection of 5 g. dextrose per kilo caused still greater diminution of the evening urine, and the secondary diuresis was not evident till the evening of April 26 and the morning of April 27.

April 30, subcutaneous injection of 1 g. levulose per kilo caused the same well-marked oliguria as dextrose.

May 3, subcutaneous injection of 2 g. levulose per kilo also caused diminution of urine, though it happened to be not so marked.

May 7, subcutaneous injection of 3 g. levulose per kilo caused more marked oliguria than either of the preceding doses, although now the levulosuria rose as high as 1.95 per cent, viz., in the evening specimen, which was the smallest in volume. Moreover, it should be noted that the dog (though in no wise sick or depressed after such a small injection) *was not thirsty*.

May 10, subcutaneous injection of 4 g. levulose per kilo caused the usual diminution of evening urine, though the levulosuria reached 4.96 per cent. As usual, the highest percentage of sugar was in the specimen which was least in volume. That is, the behavior in non-diabetes, where sugar circulates as a colloid, is exactly opposite to the behavior in diabetes, where sugar circulates as a crystalloid.

May 20, there was a subcutaneous injection of 5 g. levulose

per kilo. The same results as before appear even more clearly. The levulosuria reached 5.2 per cent. The greatest levulosuria accompanied the greatest oliguria. Nitrogen as well as water was retained. The next day began the secondary diuresis and elimination of nitrogen.

May 24, there was a subcutaneous injection of 1 g. galactose per kilo. The result was a slight galactosuria of 0.24 per cent, and a slight diminution in the evening output of water and nitrogen.

May 27, there was a subcutaneous injection of 3 g. galactose per kilo. The result was galactosuria as high as 7.3 per cent, and a slight diminution of evening urine, followed by a slight diuresis the next day. The facts seem to indicate that galactose is less firmly combined in the body than dextrose and levulose, hence is utilized less readily and has less effect in diminishing the urine. Nevertheless, a combination presumably exists, for the urine is diminished, and the specimen containing most galactose is least in volume.

May 30, there was a subcutaneous injection of 1 g. lactose per kilo. The effect upon the urine was not great. The appearance is as if the evening urine were slightly increased. Nevertheless it must be observed that the specimen which contains most lactose is smallest in volume, and the diuresis on the following day, after lactose disappeared from the urine, is far greater than during the time the urine contained lactose.

June 3, there was a subcutaneous injection of 3 g. lactose per kilo. The result was an unmistakable increase in the evening urine. Nevertheless, the specimen containing most lactose was smallest in volume, and the diuresis on the following day, after the lactose disappeared from the urine, was greater than during the period of lactosuria.

June 7, there was a subcutaneous injection of 5 g. lactose per kilo. There was a decided increase in the urine not only of that evening, but of the entire 24 hours following injection. Nevertheless, the specimen containing most lactose was notably smallest in volume, and the quantity of urine for the second 24 hours, when the lactose had nearly or completely disappeared, was decidedly greater than during the period of lactosuria.

June 13, there was a subcutaneous injection of 500 cc. saline solution. The slight increase of evening nitrogen, and the diuresis, are evident.

June 22, there was a subcutaneous injection of 500 cc. 5 per cent dextrose solution. The oliguria as compared with June 13 is notable.

June 27, there was an intravenous injection of 100 cc. 25 per cent saccharose (between 3 and 4 g. per kilo). Here, as usual after intravenous injection, the sugar behaves as a diuretic. The specimens containing most sugar are the largest in volume. Furthermore, a diuresis, in proportion to the percentage of sugar, continues till the sugar is all eliminated; there is no secondary oliguria setting in an hour or so after injection, as in the case of dextrose.

DOG 21.

Diet 200g. Bread-and-Mixture.

Date	Hour	Treatment	Water cc.	Urine		
				Quant. cc.	Sugar	Nitrogen g.
Aug. 3	9.30 A.M.		200			
	4.30 P.M.	Water by tube.	200			
	6 P.M.			220	---	
" 4	9.30 A.M.		200	355	---	
	9.45 A.M.	Intravenous injection of 100cc.25% dextrose solu.				
	11 A.M.			150	4.6%	
	12 M.			53	3.2%	
	1 P.M.			10	1.1%	
	2 P.M.			15	slight	
	3 P.M.			52	faint	
	4.30 P.M.		200	33	---	
" 5	9.30 A.M.			350	---	
" 8		Same diet. Water ad libitum, to be measured.				
" 9	4.30 P.M.		80	75	---	1.86
" 10	9 A.M.		0	150	---	2.64
	4.30 P.M.		100	55		1.5
" 11	9 A.M.	Intravenous injection of 100cc. 30% dextrose solu.	20	80	---	2.72
	11 A.M.			147	4.5%	
	12 M.			15	1.8%	
	1 P.M.			20	faint	
	3.30 P.M.			30	---	
	4.30 P.M.		80	16 (Total P.M. 228)	---	1.997
" 12	9 A.M.		20	90	---	2.7
	4.30 P.M.		30	75	---	2.11
" 13	9.30 A.M.		25	100	---	3.

Summary.

August 4, there was an intravenous injection of 100 cc. 25 per cent dextrose. The primary polyuria and secondary oliguria, with continuing glycosuria, are evident. Between 12 and 1 p.m., with a glycosuria of 1.1 per cent, the amount of urine was only 10 cc. Between 2 and 3 p.m., when the sugar had almost disappeared, the urine was 52 cc.; and from 3 to 4:30 p.m., when there was no glycosuria, the urine was 33 cc. The secondary oliguria is presumably due chiefly to change of the dextrose into the combined form. Permeability of the kidney may be a factor; but if it were the chief factor, the behavior of lactose and saccharose should be like that of dextrose, and in my experience this is not true.

August 11, there was an intravenous injection of 100 cc. 30 per cent dextrose solution. The secondary oliguria, and the discordance between glycosuria and diuresis, are apparent here also.

Summary for Dog 22 (pp. 327, 328).

December 27, a slow ($\frac{1}{2}$ hour) injection of 3 g. saccharose per kilo intravenously caused mild diuresis, without increase of nitrogen.

December 30, subcutaneous injection of 7 g. saccharose per kilo caused the usual increase in nitrogen excretion; but the volume of urine was not increased, or was actually diminished if allowance be made for the water injected. The weight indicated retention of water.

The giving of 1 to 3 g. dextrose per kilo, by mouth or subcutaneously, on the following days up to January 5, had no distinct effect upon the quantity of urine.

January 7, subcutaneous injection of 10 g. dextrose per kilo diminished the output of urine, absolutely, and especially after allowance for the water injected. This was in spite of a glycosuria of 5.6 per cent. Furthermore the dog (morning January 8) was not thirsty. On January 8 and 9, secondary diuresis occurred.

January 11, subcutaneous injection of 10 g. lactose per kilo caused a slight increase of urine, but the weight indicated no marked loss of water. Afterward, up to the morning of January 13, there was secondary oliguria.

January 14, subcutaneous injection of 10 g. saccharose per kilo caused a mild diuresis, with slight secondary oliguria.

DOG 22. Weight 6200g.

Starvation from December 18 to January 17.
100cc. water by tube at 9.30 A.M. & 4.30 P.M.

Date	Hour	Treatment	Urine		
			Quant. cc.	Sugar %	Nitro. g.
Dec. 25			114	-	1.51
" 26			105	-	1.35
" 27	9.30 A.M.	Intravenous injection of 19.3cc. 80% saccharose solution (3g. per kilo).	130	-	1.24
	4.30 P.M.		90	Pos.	
" 28	9.30 A.M.		64 (Total 24 hours 154)	-	1.07
" 29	9.30 A.M.		98	-	1.69
	4.30 P.M.		24	-	
" 30	9.30 A.M.	Subcut. injection of 43.1cc. 80% saccharose solution (7g. per kilo).	44 (Total 24 hours 68)	-	0.91
	4.30 P.M.		85	Heavy	
" 31	9.30 A.M.		38 (Total 24 hours 123)	"	1.85
	4.30 P.M.		20	Pos.	
Jan. 1	9.30 A.M.		70 (Total 24 hours 90)	-	1.71
	4.30 P.M.		60	-	
" 2	9.30 A.M.	4.72g. dextrose (1g. per kilo) per mouth.	65 (Total 24 hours 125)	-	0.77
	4.30 P.M.		85	-	
" 3	9.30 A.M.	9.4g. dextrose (2g. per kilo) per mouth.	58 (Total 24 hours 143)	-	1.12
	4.30 P.M.		76	0.7	
" 4	9.30 A.M.	Subcut. injection of 5.9cc. 80% dextrose solution (1g. per kilo).	106 (Total 24 hours 182)	-	1.07
	4.30 P.M.		54	-	
" 5	9.30 A.M.	Subcut. injection of 17.25cc. 80% dextrose (3g. per kilo).	90 (Total 24 hours 144)	-	0.89
	4.30 P.M.		70	0.48	
" 6	9.30 A.M.		46 (Total 24 hours 116)	faint	0.74
	4.30 P.M.		126	-	

DOG 22 (Continued).

Date	Hour	Treatment	Urine		
			Quant. cc.	Sugar %	Nitro. g.
Jan. 7	9.30 A.M.	Subcut. injection of 55.62cc. 80% dextrose (10g. per kilo).	106 (Total 24 hours 232)	-	
	4.30 P.M.		60	5.6	1.43
" 8	9.30 A.M.		32 (Total 24 hours 92)	0.6	
	4.30 P.M.		125	-	0.835
" 9	9.30 A.M.		135 (Total 24 hours 260)	-	
	4.30 P.M.		110		1.12
" 10	9.30 A.M.		60 (Total 24 hours 170)	-	
	4.30 P.M.		48	-	0.64
" 11	9.30 A.M.	Subcut. injection of 52.8cc. 80% lactose solution (10g. per kilo)	60 (Total 24 hours 108)	-	0.94
	4.30 P.M.		170	Heavy	0.704
" 12	9.30 A.M.		86	"	0.645
	4.30 P.M.		10	"	0.25
" 13	9.30 A.M.		80	mod.	3.4
	4.30 P.M.		55	slight	1.04
" 14	9.30 A.M.	Subcut. injection of 51.25cc. 80% saccharose (10g. per kilo).	170	-	1.
	4.30 P.M.		100	heavy	0.2
" 15	9.30 A.M.		100	heavy	0.582
	4.30 P.M.		17	faint	0.49
" 16	9.30 A.M.		96	-	0.785
	4.30 P.M.		75	-	0.26
" 17	9.30 A.M.		90	-	0.54

DOG 22.

Fixed Diet. Water ad libitum.

Date	Hour	Treatment	Urine	
			Quant. cc.	Sugar %
Jan. 25	12 M.	Subcut. injection of 542.5cc. 10% dextrose solution (10g.per kilo).		
	4.30 P.M.		90	2.15
" 26	9.30 A.M.		230	faint
" 27	9.30 A.M.		376	-
Feb. 18	12 M.	Subcut. injection of 550cc. 10% dextrose solution (10g.per kilo).		
	4.30 P.M.	Vomited part of feed.	30	5.
" 19	9.30 A.M.		100	faint
	4.30 P.M.		120	-
" 20	9.30 A.M.		200	-
" 21	9.30 A.M.		225	-
" 22	9.30 A.M.		120	-
" 23	9.30 A.M.		200	-
" 24	9.30 A.M.		160	-
	12 M.	Subcut. injection of 550cc. 0.85% NaCl solution.		
	4.30 P.M.		110	-
" 25	9.30 A.M.		715	-
" 26	9.30 A.M.		270	-
" 27	9.30 A.M.		400	-
" 28	9.30 A.M.		260	-

Summary.

January 25, with the dog receiving fixed diet and water constantly in cage, subcutaneous injection of 10 g. dextrose per kilo in 10 per cent solution caused glycosuria and oliguria, followed by polyuria after the glycosuria ended.

February 18, subcutaneous injection of dextrose caused pronounced oliguria, with subsequent secondary diuresis.

February 24, a control injection of saline solution caused diuresis within the first 24 hours, in striking contrast to the opposite effect which always occurs with dextrose.

DOG 18.

Diet 250g. Bread-and-meat mixture, fed at 5 P.M.
Water 200cc. at 9 A.M. and 5 P.M. by tube.

Date	Hour	Treatment	Urine		
			Quant. cc.	Reducing Sugar %	Nitro. g.
May 24	9 A.M. 5 P.M.		250 170	- -	
" 25	9 A.M. 5 P.M.		300 250	- -	
" 26	9 A.M. 5 P.M.		240 170	- -	
" 27	9 A.M. 5 P.M.		390 245	- -	3.825 1.38
" 28	9 A.M. 5 P.M.		194 165	- -	3.61 1.25
" 29	9 A.M. 5 P.M.		200 140	- -	4.3 0.44
" 30	9 A.M. 1 P.M. 5 P.M.	Subcut. injection of 7.88g. Saccharose (1g. per kilo) in 50% solution.	245 155 60 (Total P.M.215)	- - Slight	4.4 1.45
" 31	9 A.M. 1 P.M. 5 P.M.		210 235 43 (Total P.M.278)	faint - -	3.56 1.25
June 1	9 A.M.		295		3.91
" 2	9 A.M. 1 P.M. 5 P.M.		410 190 16 (Total P.M.206)	- - -	3.64 0.75
" 3	9 A.M. 1 P.M. 5 P.M.	Subcut. injection of 23.04g. saccharose (3g. per kilo) in 50% solution.	210 165 62 (Total P.M.227)	- slight heavy	3.73 1.14
" 4	9 A.M. 1 P.M. 5 P.M.		135 115 40 (Total P.M.155)	faint - -	3.2 1.36
" 5	9 A.M. 1 P.M. 5 P.M.		275 210 17 (Total P.M.227)	- - -	3.29 1.14

DOG 18 (Continued).

Date	Hour	Treatment	Urine			
			Quant. cc.	Reducing Sugar %	Nitro. g.	Saccharose %
June 6	9 A.M.		360	-	4.36	
	1 P.M.		165	-		
	5 P.M.		30	-		
			(Total P.M.195)		0.74	
" 7	9 A.M.	Subcut. injection of 38g. saccharose (5g. per kilo) in 50% solution.	300	-	4.26	
	1 P.M.		150	pos.		
	5 P.M.		60	"		
			(Total P.M.210)		1.12	
" 8	9 A.M.		165	-	4.43	
	1 P.M.	(Urine partly lost.)	-	-		
	5 P.M.		-	-		
" 9	9 A.M.		330	-		
	1 P.M.		190	-		
	5 P.M.		30	-		
" 10	9 A.M.		225	-		
	1 P.M.		200	-		
	5 P.M.		65	-		
" 11	9 A.M.		225	-		
	5 P.M.		165	-	1.53	
" 12	9 A.M.	Subcut. injection of 38.25g. saccharose in 50% solution (5g.per kilo).	290	-	3.3	
	1 P.M.		240	0.5		7.3
	5 P.M.		50	0.23		22
			(Total P.M.290)			1.47
" 13	9 A.M.		140	slight		3.9
	1 P.M.		80	-		0.8
	5 P.M.		40	-		faint
			(Total P.M.120)		2.82	
" 14	9 A.M.		160	-	3.16	
	1 P.M.		325	-		
	5 P.M.		14	-		
			(Total P.M.339)		1.69	
" 15	9 A.M.	Subcut. injection of 7.58g. maltose in 50% solution (1g.per kilo).	400	-	4.36	
	1 P.M.		180	-		
	5 P.M.		20	-		
			(Total P.M.200)		1.15	
" 16	9 A.M.		260	-	3.59	
	1 P.M.		200	-		
	5 P.M.		30	-		
			(Total P.M.230)		1.55	

DOG 18 (Continued).

Date	Hour	Treatment	Urine		
			Quant. cc.	Reducing Sugar %	Nitro. g.
June 17	9 A.M. 1 P.M. 5 P.M.		385 135 40 (Total P.M.175)	- - -	3.69 1.06
" 18	9 A.M. 1 P.M. 5 P.M.		255 133 40 (Total P.M.173)	- - -	3.65 1.185
" 19	9 A.M. 1 P.M. 5 P.M.	Subcut. injection of 22.34g.maltose in 50% solution (3g.per kilo).	265 120 20 (Total P.M.140)	- faint slight	3.56 0.9
" 20	9 A.M. 1 P.M. 5 P.M.		180 180 26 (Total P.M.206)	- - -	3.13 2.29
" 21	9 A.M. 1 P.M. 5 P.M.		240 243 55 (Total P.M.298)	- - -	3.55 1.48
" 22	9 A.M. 1 P.M. 5 P.M.	Subcut. injection of 38.25g. maltose in 50% solution (5g.per kilo)	300 100 18 (Total P.M.118)	- 0.92 (maltose) 0.74 (maltose)	3.57 1.1
" 23	9 A.M. 1 P.M. 5 P.M.		280 90 90 (Total P.M.180)	faint - -	4.3 1.75
" 24	9 A.M. 1 P.M. 5 P.M.		320 170 70 (Total P.M.240)	- - -	4.76 1.39
" 25	9 A.M. 5 P.M.		380 185	- -	3.5
" 26	9 A.M. 5 P.M.		315 245	- -	
" 27	9 A.M. 5 P.M.		300 240	- -	

DOG 18 (Continued).

Date	Hour	Treatment	Urine		Water cc.
			Quant. cc.	Reducing Sugar %	
June 28	9 A.M.	Subcut. injection of 140cc. 80% lactose (15g. per kilo).	310	-	
	1 P.M.		200	12.4 (lactose)	
	5 P.M.		50	22.2 (lactose)	
" 29	9 A.M.		350	15.4 (lactose)	
	1 P.M.		90	8.9 (lactose)	
	5 P.M.		75	7 (lactose)	
" 30	9 A.M.		305	1.09 (lactose)	
	5 P.M.		100	slight	
July 1	9 A.M.		270	faint	
	5 P.M.		110	"	
" 2	9 A.M.	Water by tube discontinued. Measured drinking water to begin.	272	-	
	5 P.M.		115	-	0
" 3	9 A.M.		200	-	330
	5 P.M.		95	-	255
" 4	9 A.M.		342	-	190
	5 P.M.		135	-	233
" 5	9 A.M.		300	-	300
	5 P.M.		135	-	305
" 6	9 A.M.		375	-	380
	5 P.M.		110	-	240
" 7	9 A.M.	Subcut. injection of 140cc. 80% lactose solution.	210	-	160
	1 P.M.		635	9.2 (lactose)	950
	5 P.M.		95	19.3 (lactose)	380
" 8	9 A.M.		530	5.4 (lactose)	450
	1 P.M.		165	1.1 (lactose)	0
	5 P.M.		90	0.47 (lactose)	0
" 9	9 A.M.		245	-	110
	5 P.M.		110	-	300
" 10	9 A.M.		235	-	

Summary.

May 30, subcutaneous injection of 1 g. saccharose per kilo had but little effect upon the urine. The nitrogen, especially of the evening specimen, appears a little increased. The quantity of urine was greater than on some preceding days, but less than on May 25 or 27. The weight indicated retention of water. Moreover, as soon as the cane-sugar disappeared from the urine, diuresis began, so that the evening urine of May 31 was more than the evening urine of May 30, and the total for the first 24 hours of sugar-free urine was nearly 150 cc. more than the total for the 24 hours of sugar-containing urine.

June 3, there was a subcutaneous injection of 3 g. saccharose per kilo. The 1 p.m. urine was not as much as on the day preceding, nor as much as on June 5. The total evening specimen, as compared with the preceding day, is increased, but the increase is not enough to cover the quantity of water injected with the sugar. The total urine for the 24 hours following injection is diminished. The body-weight was increased. Beginning June 5, diuresis occurred, with a corresponding drop in weight.

June 7, there was a subcutaneous injection of 5 g. saccharose per kilo. The 1 p.m. urine was less than on the day preceding. The total evening specimen appears a trifle increased, but the increase is far from equalling the amount of water injected with the sugar. The 24-hour total of urine was diminished. Though all these experiments were done with a fixed intake of water, yet today's results are not due to lack of water, for at 4 p.m. the dog, though lively and hungry, would not drink. The secondary diuresis could not be followed, owing to diarrhea and loss of urine.

The same injection (5 g. saccharose per kilo) was repeated on June 12. In this case, the 1 p.m. and total evening urine showed a pronounced increase. But by referring back to the period before injections (May 24–28), it is seen that the evening urine ranged from 170 to 250 cc. The increase today therefore may well be covered by the water injected with the sugar. The evening nitrogen was less than on the day before. The total urine for the 24 hours following injection was diminished. The retention of water was indicated by the increase of weight. On the next day, the retention was more marked, and the weight still further increased. Then (during June 14) began diuresis far surpassing the output while the urine contained sugar, the retained nitrogen came out along with the water, and the weight dropped correspondingly.

June 15, there was a subcutaneous injection of 1 g. maltose

per kilo. No maltosuria occurred. Both the urine and the nitrogen, for both the evening and the 24-hour specimens, were less on the first day following injection (June 15–16) than on the second day following injection (June 16–17).

June 19, there was a subcutaneous injection of 3 g. maltose per kilo. Slight mellituria occurred. There was a pronounced diminution both of urine and of nitrogen in this evening specimen, which contained maltose. The 24-hour urine was diminished. The weight was increased. The urine was more on June 20 than on June 19; but the real diuresis came on June 21, two days after the injection.

June 22, there was a subcutaneous injection of maltose corresponding to the saccharose injection of June 12 (then 5 g. per kilo). Moderate maltosuria resulted. The urine was decreased, both for the evening, and for the 24 hours. The weight was increased. The oliguria continued the next day. Two days after the injection, diuresis began, and the weight dropped.

June 28, there was a subcutaneous injection of 15 g. lactose per kilo. Lactosuria ran as high as 22.2 per cent; and the 5 p.m. specimen containing this percentage was less in volume than the 1 p.m. specimen, which contained a smaller percentage. Though the solution injected amounted to 140 cc., the urine was little if any increased. The absence of diuresis during the night and the next day could only partly be accounted for by the diminished eating. The failure to eat, and the diarrhea, partly explain the loss of weight. The usual secondary diuresis remained absent, probably because of diarrhea.

The same subcutaneous injection (15 g. lactose per kilo) was repeated on July 7, with water supplied ad libitum. The great thirst and polyuria are evident. The evening urine, which contained the most lactose, was the least in volume. Diarrhea and vomiting may partly explain the loss of weight and the absence of secondary diuresis.

Nevertheless, the fact must not be overlooked that in these two large injections (June 29 and July 7) lactose given subcutaneously actually behaved for the most part like a diuretic. If it always behaved this way, causing primary polyuria and secondary oliguria, it would have to be classified as a diuretic. It behaves as if the very large doses were beyond the power of the body to combine fully, and as if considerable free lactose entered the circulation and there showed its characteristic effects. A similar result has sometimes been noted from large injections of saccharose and lactose in the preceding dogs.

DOG 48.

Diet 225g. Bread-and-meat mixture, fed 4.30 P.M.
200cc. water 9.30 A.M. and 4.30 P.M. by tube.

Date	Hour	Weight g.	Treatment	Urine		
				Quant. cc.	Sugar	Nitro. g.
June 6	9.30 A.M.	9550		290		3.75
	1 P.M.			210		
	4.30 P.M.			20		0.75*
" 7	9.30 A.M.	9540		275		3.77
	1 P.M.			210		
	4.30 P.M.			16		0.75
" 8	9.30 A.M.	9570	Subcut. injection of 500cc. 0.85% NaCl solution.	280		3.55
	1 P.M.			180		
	4.30 P.M.			85		1.11
" 9	9.30 A.M.	9640		630		4.1
	1 P.M.			280		
	4.30 P.M.			35		0.78
" 10	9.30 A.M.	9520		270		3.42
	1 P.M.			130		
	4.30 P.M.			227		0.71
" 11	9.30 A.M.	9360	Diet increased to 250g. bread-and-meat mixture.	255		3.7
	4.30 P.M.			165		0.68
" 12	9.30 A.M.	9350		350		4.6
	1 P.M.			160		
	4.30 P.M.			25		1.01
" 13	9.30 A.M.	9400	Subcut. injection of 500cc. 0.85% NaCl solution.	250		3.4
	1 P.M.			55		
	2 P.M.			155		
	4.30 P.M.			120		1.76
" 14	9.30 A.M.	9500		550		4.57
	1 P.M.			240		
	4.30 P.M.			35		1.09
" 15	9.30 A.M.	9215		400		3.8
	1 P.M.			170		
	4.30 P.M.			35		1.07
" 16	9.30 A.M.	9240		320		4.33
	1 P.M.			155		
	4.30 P.M.			35		1.06
" 17	9.30 A.M.	9200	Subcut. injection of 500cc. 5% dextrose solution.	330	-	4.24
	1 P.M.			47	-	
	2 P.M.			12	faint	
	3.30 P.M.			20	very faint	

*Afternoon Nitrogen always represents total for urine after 9.30 A.M.

DOG 48 (Continued).

Date	Hour	Weight	Treatment	Urine		
				Quant. cc.	Sugar %	Nitro. g.
June 17 continued	4.30 P.M.			90	-	1.21
June 18	9.30 A.M.	9400		625		5.89
	1 P.M.			210		
	4.30 P.M.			65		1.155
" 19	9.30 A.M.	9190		380		4.07
	1 P.M.			190		
	4.30 P.M.			30		1.04
" 20	9.30 A.M.	9110	Subcut. injection of 500cc. solution containing 0.85% NaCl & 5% dextrose.	210	-	3.49
	1 P.M.			78	-	
	2 P.M.			10	-	
	4.30 P.M.			14	-	1.32
" 21	9.30 A.M.	9305		500	-	4.94
	1 P.M.			250		
	4.30 P.M.			90		1.06
" 22	9.30 A.M.	9200		420		4.08
	1 P.M.			190		
	4.30 P.M.			35		1.14
" 23	9.30 A.M.	9050		300		4.1
	1 P.M.			150		
	4.30 P.M.			45		1.17
" 24	9.30 A.M.	9030	Subcut. injection of 500cc. 10% saccharose solution.	250	-	4.33
	1 P.M.			210	(reducing) 0.6 saccharose 10.1	
	4.30 P.M.			90	(reducing) 1.6 saccharose 16.6	1.28
" 25	9.30 A.M.	9740		150	(reducing) 0.6 saccharose 2.7	1.12
	4.30 P.M.			345	-	2.73
" 26	9.30 A.M.	9000		720	-	6.33
	4.30 P.M.			320		1.2
" 27				280		3.3

Summary for Dog 48.

June 8, there was a subcutaneous injection of 500 cc. saline solution, and another of the same on June 13.

June 17, there was a subcutaneous injection of 500 cc. 5 per cent dextrose solution (in distilled water). The oliguria as compared with the saline injections is obvious, also the secondary polyuria the next day.

June 20, for the sake of a still more rigid comparison, there was a subcutaneous injection of 500 cc. saline solution containing 5 per cent dextrose. The diminution of the evening urine as compared with the pure saline injections, and the secondary diuresis the next day, are again obvious.

June 24, there was a subcutaneous injection of 500 cc. 10 per cent saccharose solution. The evening urine showed no diuresis as compared with the saline days, and the nitrogen output was only a trifle elevated. The urine of the next morning was markedly diminished in volume and in nitrogen, so that the net result for the 24 hours was a retention of both water and nitrogen, from saccharose as compared with saline. Then the following evening, after the saccharose had practically disappeared from the urine, the rush of retained substances began, and continued till the evening of June 26. The record of body-weight tells the story very clearly.

DOG 54.

Starvation from June 17 to June 26.
Water 200cc. 9.30 A.M. and 4.30 P.M., by tube.

Date	Hour	Weight	Treatment	Urine		
				Quant. cc.	Sugar	Nitrogen g.
June 20	9.30 A.M.	9180		170		1.56
	4.30 P.M.			178		1.24
" 21	9.30 A.M.	9020	Subcut. injection of 500cc.0.85% NaCl solu.	170	-	1.66
	1 P.M.			165	-	
	4.30 P.M.			50	-	1.36*
" 22	9.30 A.M.	9120		390	-	2.06
	1 P.M.			250		
	4.30 P.M.			60		0.76
" 23	9.30 A.M.	8820		260		1.59
	1 P.M.			150		
	4.30 P.M.			25		0.94
" 24	9.30 A.M.		Subcut. injection of 500cc.10% lactose solu.	190		1.535
	1 P.M.			145	12.8% (lactose)	
	4.30 P.M.			70	15.3% (lactose)	0.59*
" 25	9.30 A.M.	9080		180	8.2% (lactose)	1.22
	4.30 P.M.			360	slight	2.26
" 26		8430		500	-	2.21

*Afternoon nitrogen always represents total for urine after 9.30 a.m.

Summary for Dog 54.

June 21, there was a subcutaneous injection of 500 cc. saline solution.

June 24, there was a subcutaneous injection of 500 cc. 10 per cent lactose solution. The evening urine was the same as after the saline injection. But the urine of the following morning was much less than after saline; so that the net result for the 24 hours was a retention of water, as shown by the weight. These things occurred in spite of the high percentages of lactose in the urine. After the lactose had nearly or quite disappeared from the urine, the evening specimen of June 25 and the morning specimen of June 26 showed strong secondary polyuria and increase of nitrogen.

DOG 28.

Date	Hour	Weight g.	Treatment	Water	Urine	
					Quant. cc.	Sugar
Mar. 11	10 A.M.	7940		ad libitum	560	-
" 12	10 A.M.	8000		"	210	-
" 13	10 A.M.	8020		"	360	-
" 14	10 A.M. 11.30	8000	Subcut. injection of 360cc. 20% dextrose solution (9g. per kilo).	"	330	-
	1.45 P.M. 3 P.M.		Etherized for obtaining blood.		40	-
	7.30 P.M.		Blood-sugar=0.303%.		110	0.9%
" 15	10 A.M.	8540		"	80	faint
" 16	10 A.M.	7860		"	980	-
" 17		7965		"	360	-
" 18			Measured drinking water to begin.	"	300	-
" 19	10.30 A.M. 12 M. 5 P.M.	7800		 160 75	275	-
" 20	10.30 A.M. 12 M. 5 P.M.	7590		100 30 80	240	-
" 21	10.30 A.M. 12 M. 5 P.M.	7650		20 25 200	220	-
" 22	10.30 A.M. 12 M. 5 P.M.	7740		0 125 0	300	-
" 23	10.30 A.M.	7625		330	460	-
" 24	10.30 A.M. 12 M. 5 P.M.	7735	No feed today.	50 45 0	330	-
" 25	10.30 A.M. 12 M. 5 P.M.	7350		 210 90	190	-
" 26	10.30 A.M.			240	410	-
" 27	10.30 A.M. 12 M. 5 P.M. 8 P.M.	7840		 75 145	370 110	- -

DOG 28 (Continued).

Date	Hour	Weight g.	Treatment	Water	Urine	
					Quant. cc.	Sugar
Mar. 28	10.30 A.M.	7760	No feed today Subcut. injection of 155.2cc. 50% dextrose (10g. per kilo). Injection of 155.2cc. 25% dextrose into peritoneum (5g. per kilo). Total 15g. per kilo.	50	235	-
	11.45 A.M.			150		
	12.30 P.M.			50	28	Mod.
	1.20 P.M.			65		
	2 P.M.			30		
	3.30 P.M.			95	1.5	Heavy
	4 P.M.		Blood-sugar = 0.248%.			
	5 P.M.			170	0.3	"
	5.30 P.M.			55		
	8 P.M.			0		
" 29	10.30 A.M.	8140		10	6	Mod.
	5 P.M.			150	15	slight
	8 P.M.			100		
" 30	10.30 A.M.	7500		100	740	-
" 31					800	-
Apr. 1					speci-men	-

Summary.

The dextrose tolerance of this dog was a little above the average. On March 14, subcutaneous injection of 9 g. dextrose per kilo caused only a slight glycosuria, and this was perhaps due to the ether. The marked hyperglycemia will be noted, along with the great diminution of urine, though the dog was drinking enormous quantities, as proved by the sudden shooting up of her weight. Presumably therefore, the blood-sugar was in firmly combined condition, and was acting as a colloid in the circulation. The oliguria continued fully 24 hours, till the excess of sugar was stored or disposed of; then on March 16 came the flood of retained water, and the corresponding drop in weight.

To escape the error due to the diminished eating of the animal on injection days, March 24 was used as a fast-day, for control.

March 28 was another fast-day, with injection of 10 g. dextrose per kilo subcutaneously and 5 g. dextrose per kilo into the peritoneum. The result was not only diarrhea, but also passage of

DOG 34.

Diet 225g. Bread-and-meat Mixture, at 5 P.M.
Water 200cc. at 9.30 A.M. and 5 P.M. by tube.

Date	Hour	Treatment	Urine		
			Quant. cc.	Sugar %	Nitro. g.
Mar. 12	9.30 A.M.		575	-	
" 13	" "		520	-	
" 14	" "		420	-	
" 15	" "		400	-	
	11.25 A.M.		170	-	
	11.30 A.M.	Intravenous injection of 49.6cc. 50% dextrose solution (4g. per kilo).			
	12 M.		252	3.2	
	12.30 P.M.	Pain and worry inflicted,	16	7.3	
	1 P.M.	and dog kept tied out on	2	0.3	
	2 P.M.	back from 11 A.M. to	3	0.45	
	5 P.M.	5 P.M.	10	slight	
	8.15 P.M.		40	faint	
" 16	9.30 A.M.		210	-	
" 17	" "		320	-	
" 18	" "		600	-	
" 19	" "		350	-	
" 20	" "		500	-	
" 21	" "		520	-	
" 22	" "		440	-	
" 23	" "		535	-	
" 24	9.30 A.M.		570	-	
	5 P.M.		154	-	0.88
" 25	9.30 A.M.		270	-	3.47
	5 P.M.		160	-	0.9
" 26	9.30 A.M.		255	-	3.55
	5 P.M.		175		0.82
" 27	9.30 A.M.		260	-	3.8
	5 P.M.		180		0.77
" 28	9.30 A.M.	Intravenous injection of 150cc. 25% dextrose solution (6g.per kilo).	250	-	3.79
	9.45 A.M.		80	4.4	
	1 P.M.		200	1.4	
	5 P.M.		70	slight	1.14*
" 29	9.30 A.M.		180	-	3.43
	5 P.M.		180	-	1.06
" 30	9.30 A.M.		250	-	3.5
	1 P.M.		150	-	
	5 P.M.		50	-	0.89
" 31	9.30 A.M.	Intravenous injection of 51.6cc. 25% dextrose solution (2g.per kilo).	250	-	3.865
	11 A.M.		170	1	
	12 M.		60	0.16	
	1 P.M.		25	slight	
	5 P.M.		58	faint	1.48

DOG 34.

Date	Hour	Treatment	Urine		
			Quant. cc.	Sugar %	Nitro. g.
Apr. 1	9.30 A.M.		500	-	3.09
	11 A.M.		130	-	
	12 M.		6	-	
	1 P.M.		7	-	
	5 P.M.		33	-	0.9*
" 2	9.30 A.M.		285	-	3.42
	1 P.M.		170	-	
	5 P.M.		34	-	1.09
" 3	9.30 A.M.		320	-	3.42
	1 P.M.		145	-	
	5 P.M.		20	-	0.97
" 4	9.30 A.M.		240	-	3.52
" 9	5 P.M.		205	-	0.63
" 10	10.30 A.M.		390	-	3.84
	5 P.M.		160	-	0.92
" 11	9.30 A.M.	Subcut. injection of 24cc. 80% lactose solution (3g.per kilo).	290	-	3.45
	1 P.M.		150	7.8	
	5 P.M.		40	15.7	1.
" 12	9.30 P.M.		250	faint	4.25
	1 P.M.		160	"	
	5 P.M.		45	-	1.61
" 13	9.30 A.M.		340	-	
	1 P.M.		160	-	
	5 P.M.		18	-	
" 14	9.30 A.M.	Subcut. injection of 24cc. 80% saccharose solution (3g.per kilo).	270	-	
	1 P.M.		150	heavy	
	5 P.M.		60	"	
			(Total P.M. 210)		
" 15	9.30 A.M.		500	Mod.	
	1 P.M.		50	-	
	5 P.M.		25	-	
" 16	9.30 A.M.		130	-	
	1 P.M.		210	-	
	5 P.M.		30	-	
" 17	9.30 A.M.		280		
	1 P.M.		150		
	5 P.M.		50		
" 18	9.30 A.M.		330	-	
	9.35 A.M.		1	-	
	9.35-9.50 A.M.	Injection of 203.2cc. 25% dextrose solution into peritoneum (8g. per kilo).			
	9.50 A.M.		1.5	0.5	
	10.20 A.M.		1.25	16.6	
	10.40 A.M.	Blood-Sugar = 0.42%			
	12 M.		0.5	10.4	
	5 P.M.		0		
" 19	9.30 A.M.		28	-	

*Afternoon nitrogen always represents total for urine after 9.30 A.M.

sugar by rectum. The animal drank and retained large quantities of water; the glycosuria was heavy; and hyperglycemia persisted even to the latter part of the afternoon, as the test showed. Yet there was almost anuria. It is in accord with the rule that in a normal animal (except intravenously), the larger the dose of dextrose and the higher the glycosuria, the less is the quantity of urine.

Summary for Dog 34.

The intravenous injections of March 15, 28, and 31 show the diuretic effects of dextrose in doses from 2 to 6 g. per kilo. That of March 15 shows the negative effects of pain and worry; the diuresis was the same as without them. Polyuria always ceases while glycosuria continues. Even a glycosuria of 7.3 per cent does not then involve polyuria.

On April 11, subcutaneous injection of 3 g. lactose per kilo caused no diuresis, but an increase of nitrogen. The increase of urine came after the lactose had nearly disappeared from the urine, that is, in the 24 hours of April 12–13.

On April 14, subcutaneous injection of 3 g. saccharose per kilo resulted in very slight increase of urine, until the heaviest saccharosuria was over. The 1 p.m. specimen was actually diminished as compared with the two preceding days. The real diuresis came during the night, when the proportion of sugar was less. During April 15 there was secondary oliguria, which is rather unusual after subcutaneous saccharose injection. On the whole, the diuretic tendency of saccharose was somewhat greater than usual.

On April 18, there was an injection of 8 g. dextrose per kilo into the peritoneum. The glycosuria rose as high as 16.6 per cent. This is the highest percentage which I have found in a normal animal; and accordingly, the oliguria was likewise maximum, almost to anuria. The blood-sugar at the same time was 0.43 per cent.

The following experiments concern partially depancreatized dogs, which are not diabetic but have a reduced sugar-tolerance. The operative procedures will be described in a later chapter. As a rule, the pancreatic duct is left uninjured, and the partially depancreatized animal retains good digestion.

DOG 32. Weight 6 kilos.

Diet 250g. Bread-and-Meat Mixture, at 5 P.M.
Water 200cc. 9.30 A.M. and 5 P.M. by tube.

Date	Hour	Treatment	Urine		
			Quant. cc.	Sugar %	Nitrogen g.
Apr. 5	9.30 A.M.		390	-	1.94
	5 P.M.		120	-	0.47
" 6	9.30 A.M.		310	-	1.87
	1 P.M.		180	-	
	5 P.M.		10	-	0.405*
" 7	9.30 A.M.	Subcut. injection of 24.2cc. 50% dextrose solution (2g. per kilo).	210	-	1.67
	1 P.M.		130	slight	
	5 P.M.		20	-	0.59
" 8	9.30 A.M.		96	-	1.44
	5 P.M.		215	-	0.52
" 9	9.30 A.M.		440	-	1.88
	5 P.M.		190	-	0.42
" 10	9.30 A.M.	35.7g. dextrose per mouth (6g. per kilo).	280	-	1.73
	1 P.M.		50	3.7	
	5 P.M.		90	0.21	0.41
" 11	9.30 A.M.		310	-	1.42
	5 P.M.		170	-	0.46
" 12	9.30 A.M.		290	-	1.91
	1 P.M.		220	-	
	5 P.M.		8	-	0.51
" 13	9.30 A.M.	Subcut. injection of 500cc. 0.85% NaCl solution.	230	-	1.74
	1 P.M.		220	-	
	5 P.M.		100	-	0.64
" 14	9.30 A.M.		480	-	2.13
	1 P.M.		150	-	
	5 P.M.		70	-	0.53
" 15	9.30 A.M.		360	-	1.83
	1 P.M.		300	-	
	5 P.M.		6	-	0.43
" 16	9.30 A.M.	Subcut. injection of 500cc. 5% dextrose solution.	210	-	1.53
	1 P.M.		70	2.7	
	5 P.M.		70	slight	0.44
" 17	9.30 A.M.		530	-	2.23
	1 P.M.		250	-	
	5 P.M.		80	-	0.93
" 18	9.30 A.M.		380	-	1.32

*Afternoon nitrogen always represents total for urine after 9.30 A.M.

Summary for Dog 32.

About seven-eighths of the pancreas had been removed on February 14. Contrary to the rule with the other dogs, the duct had been destroyed, so that digestion was rather poor.

April 7, there was a subcutaneous injection of 2 g. dextrose per kilo. The lowered tolerance was shown by a slight glycosuria. The evening urine was diminished as compared with the day before; but the effect was still greater in reducing the urine of the next morning.

Remarks. — 1. Presumably there is no one definite colloid-sugar compound, but rather a complex which may exist in many different degrees of saturation. Looser and firmer bindings of sugar help to explain many variations of tolerance and of glycosuria. The sugar that is most firmly bound, most thoroughly saturated with amboceptor, is probably the most quickly and easily assimilable. As the proportion of sugar in the complex increases, and that of amboceptor decreases, the sugar becomes more slowly and difficultly assimilable by the tissues. But it is still a colloid, and still acts upon the kidney as a colloid. This supposition is in accord with the behavior of partially depancreatized animals to sugar. Such an animal has enough amboceptor to supply its actual necessities; it gets along on a rather narrow margin, but yet it is safe from diabetes. When dextrose is injected in such an animal, there is not enough amboceptor, nor can the small fragment of pancreas supply amboceptor rapidly enough, to bind the sugar as firmly as in a normal animal. That is, the sugar is less firmly combined than normal; the tissues can therefore utilize it less rapidly than normal. It reaches a higher percentage in the blood than in a normal animal; hence glycosuria results from smaller doses. But the blood-sugar is a colloid nevertheless. Therefore the urine is diminished, just as in a normal animal; and in some cases, as will be noted, the effect upon the urine may possibly be greater than in normal animals. On the other hand, increased blood-sugar and looser binding may approximately offset each other, so that the effect upon the diuresis is about the same as in a normal animal.

2. A form of tachyuria was here observable. Water "ran through" the animal with abnormal rapidity. After the giving of 200 cc. water by tube at 9:30 a.m. and 5 p.m., whenever the march of the diuresis has been accurately followed during the day, an abnormal rate is apparent, viz., an excessive volume of the

1 p.m. specimen as compared with the 5 p.m. specimen. For example, on April 6, the 1 p.m. urine is 180 cc., the 5 p.m. urine only 10 cc.; that is, a dog whose supply of water is ample, passes only 10 cc. urine in 4 hours. Skipping injection-days, etc., we see that on April 12 the 1 p.m. urine was 220 cc., and the 5 p.m. specimen only 8 cc. Furthermore, there was always the same difference in the character of these two specimens; the 1 p.m. urine was almost water-pale; the 5 p.m. urine was dark and heavy, as if the animal were receiving insufficient water. On April 15, the 1 p.m. urine was 300 cc.; the 5 p.m. specimen was 6 cc. Lack of time prevented studying the phenomenon. Normal dogs have never shown such disparity between the noon and evening urine, nor have other partially depancreatized dogs been observed to show it. But if I had studied other dogs in which the pancreatic duct had been ligated along with partial pancreatectomy, the anomaly might have been discovered in others. It may possibly be interpreted as some abnormality in the "binding" of water or salts in such an animal, possibly dependent upon deficiency or abnormality of amboceptor substances for salts or possibly for water. The process in this dog seems analogous to the abnormally rapid elimination of ingested water which authors have described in some human patients. In the experiment of April 7, the facts just narrated explain the behavior of the evening urine. Much of the morning water was eliminated before the subcutaneous injection had produced its effect upon the blood. Then, the colloidal sugar held the water in the vessels more firmly than usual, so that the disparity between the 1 p.m. and 5 p.m. specimens was less than usual in this dog.

April 10, there was intrastomachal introduction of 6 g. dextrose per kilo. The glycosuria reached 3.7 per cent in the 1 p.m. urine. Accordingly, this specimen, ordinarily so large, became less than the 5 p.m. quantity, which contained less sugar. The total evening urine was diminished.

April 13, there was a subcutaneous injection of 500 cc. saline solution. No abnormality was apparent in the manner of disposing of it.

April 16, there was a subcutaneous injection of 500 cc. 5 per cent dextrose solution. The glycosuria reached 2.7 per cent. The evening urine was diminished, even below the ordinary quantity on days without injection. The next morning, when the urine was sugar-free, diuresis appeared.

DOG 63. (See Protocol).

Starvation from June 27 to July 5
Water 200cc. at 9 A.M. and 4.30 P.M. by tube.

Date	Hour	Treatment	Urine	
			Quant. cc.	Sugar %
June 28	9 A.M.		140	-
	4.30 P.M.		90	-
" 29	9 A.M.		250	-
	4.30 P.M.		100	-
" 30	9 A.M.	Subcut. injection of 500cc. 0.85% NaCl solution.	200	-
	1 P.M.		135	-
	4.30 P.M.		45	-
July 1	9 A.M.		400	-
	4.30 P.M.		228	-
" 2	9 A.M.		167	-
	4.30 P.M.		100	-
" 3	9 A.M.	Subcut. injection of 500cc. 10% dextrose solution.	175	-
	1 P.M.		130	3.6
	4.30 P.M.		12	7.3
" 4	9 A.M.		325	-
	4.30 P.M.		255	-
" 5	9 A.M.		155	-

Summary for Dog 63.

About four-fifths of the pancreas had been removed on June 13. The duct was undisturbed, and the animal's digestion good. On bread diet the dog showed no glycosuria.

June 30, there was a subcutaneous injection of 500 cc. saline solution.

July 3, there was a subcutaneous injection of 500 cc. 10 per cent dextrose solution. Glycosuria ranged from 3.6 per cent to 7.3 per cent. The oliguria as compared with June 30 is evident. The specimen containing most dextrose was least in volume. The next day, after the sugar had disappeared from the urine, the usual abundant secondary diuresis set in.

DOG 17.

Starvation from March 17 to 29.
Water ad libitum.

Date	Hour	Treatment	Water	Urine		
				Quant. cc.	Sugar	Nitrogen g.
Mar. 17	9.30 A.M.		90	340	-	
" 18	" "		150	400	-	5.41
" 19	" "		120	160	-	3.16
" 20	" "		160	110	-	2.77
" 21	" "		55	70	-	2.43
	5 P.M.		85			
" 22	9.30 A.M.		115	72	-	2.43
	5 P.M.		40			
" 23	9.30 A.M.		85	87	-	2.18
	5 P.M.			35	-	0.85
" 24	9.30 A.M.	Subcut. injection of 30.64cc.50% dextrose solution (2g. per kilo).	40	32	-	1.01
"	12.30 P.M.		165			
	5 P.M.		0	20	1.2%	0.66
" 25	9.30 A.M.		0	30	slight	0.87
	12.30 P.M.		75			
	5 P.M.		25	30	very faint	0.485
" 26	9.30 A.M.		75	27	-	0.68
	5 P.M.			15	-	0.505
" 27	9.30 A.M.	Subcut. injection of 88cc. 50% dextrose solution (6g. per kilo).		35	-	1.02
	12.30 P.M.		260			
	2 P.M.		75			
	5 P.M.		55	45	5.6%	0.404
" 28	9.30 A.M.		0	120	-	1.82
	5 P.M.		0	52	-	1.29
" 29	9.30 A.M.		0	48	-	1.24

Summary for Dog 17.

March 9, somewhat more than four-fifths of the pancreas had been removed. The duct was undisturbed, and the animal's digestion perfect. On bread diet the dog showed no glycosuria.

March 24, there was a subcutaneous injection of 2 g. dextrose per kilo. Glycosuria was up to 1.2 per cent, and lasted for somewhere between 24 and 36 hours. The dog was allowed water freely. The drinking was increased, and the urine was decreased. This result under such conditions is worthy of special notice. The effect upon the urine was greater than generally occurs in normal fasting dogs, in which an injection of 2 g. per kilo causes no glycosuria.

March 27, there was a subcutaneous injection of 6 g. dextrose per kilo. The glycosuria reached 5.6 per cent. The amount of water drunk was multiplied. The increase in the urine was insignificant. The retention of water was proved by the weight. By the following morning, the urine had become sugar-free, and diuresis accordingly set in, while the dog drank nothing.

It will be observed in all the partially depancreatized, non-diabetic animals, that the paradoxical law of dextrose holds unbroken. The *apparent* tolerance is low; but the dogs are not diabetic, hence the more sugar is given, the more can be used. The *real* tolerance is still infinite.

B. Experiments with Diabetic Animals.

Most of the dogs here presented are made diabetic by a method to be described in Chapter X. For comparison, one completely depancreatized animal is introduced.

DOG 19.

Water ad libitum.

Date	Hour	Treatment	Meat eaten g.	Urine			Feces Nitro. g.
				Quant. cc.	Sugar %	Nitro. g.	
Mar. 13	9.15 A.M.		1000	460	4.	11.28	1.26
" 14	" "		750	835	4.8	19.17	6.15
" 15	" "		800	800	4.8	19.62	6.62
" 16	" "			780	7.3	15.59	0
	12.45 P.M.	Blood-sugar 0.326%.		42	2.1		
	1.15 P.M.		650	22	1.		
" 17	9.15 A.M.		800	730	2.6	16.03	4.85
	5.30 P.M.			190	1.8	3.51	
" 18	9.15 A.M.	Subcut. injection of 35cc. 50% dextrose solution (3g. per kilo).	550	438	3.2	10.3	6.5
	5.30 P.M.			465	4.	5.02	
" 19	9.15 A.M.		460	460	3.1	9.84	5.8
	5.30 P.M.			380	3.2	5.91	
" 20	9.15 A.M.		810	375	3.4	6.91	3.
	5.30 P.M.			270	3.3	4.11	
" 21	9.15 A.M.			665	3.8	12.91	4.18

Summary for Dog 19.

The dog had been diabetic since February 7.

March 18, there was a subcutaneous injection of 3 g. dextrose per kilo. The result was not only an increase of glycosuria, but also an increase of the evening urine to more than double what it had been the evening before. An aggravation of the diabetes seemed to be present during the next day or two; and since other dogs have behaved similarly, the occurrence is presumably not a mere coincidence. The urine of the evening before injection contained 3.42 g. dextrose. The urine of the evening following injection contained 18.6 g. dextrose. The sugar excretion of the day following injection was also high. The urinary nitrogen was increased during the diuresis. Owing to spontaneous fluctuations, exact figuring may be omitted; but the record apparently indicates that within the day or two following injection, the excretion of sugar, over and above what was usual in this dog, amounted to more than the dose injected.

Throughout the diuresis, it will be noted that the percentage of sugar in the urine is even lower than in several normal dogs, in which oliguria always accompanied the glycosuria.

DOG 49.

Water ad libitum, measured.

Date	Hour	Treatment	Water cc.	Urine	
				Quant. cc.	Sugar %
June 2	9.45 A.M.		380	305	2.8
	11 A.M.	Received blood transfusion on account of weakness.		7	0.45
	12 M.			16	0.35
	1 P.M.			30	0.4
	5 P.M.		245	65	0.54
" 3	9.45 A.M.		220	250	mod.
				10	slight
	11.15 A.M.	Subcut. injection of 68cc. 80% dextrose solution (12.5g. per kilo).		30	mod.
	12 M.			40	6.
	1 P.M.			70	6.
	2 P.M.		500	135	4.
	3 P.M.			65	2.6
	4 P.M.			70	4.
	5 P.M.			47	6.
	8 P.M.		880	33	4.6
	11 P.M.			10	2.
" 4	9.45 A.M.		250	210	3.65
	1 P.M.			40	3.

Summary for Dog 49.

This dog was diabetic since May 22. Distemper, starvation, and other factors had caused her to fail rapidly. On June 2 she was ready to die, and accordingly received a direct transfusion of all the blood obtainable from a normal dog considerably larger than herself. She was perceptibly strengthened thereby. The amount of amboceptor received with the blood was negligible (in agreement with Hedon).

This experiment was performed to answer the possible argument that the failure of diuresis after a large injection of dextrose in a normal dog, is due to general prostration and weakness, or "osmotic" injury to the kidney or any other organ. Therefore on June 3, this very weak dog received a subcutaneous injection of 12½ g. dextrose per kilo. In consequence, the total urine up to 5 p.m. was 427 cc. The total urine from that time to 9:30 the next morning was 253 cc. And the dog died of weakness between 1 and 3 p.m. that day.

Undoubtedly a stronger diabetic dog would have shown greater diuresis. But even here, the extreme weakness did not prevent the diuresis caused by sugar circulating as a crystalloid.

Summary for Dog 20.

The dog was diabetic since December 7, and was in very good condition.

December 27, there was an intravenous injection of 3 g. dextrose per kilo. The effect as usual was diuresis. But the effect was greater than in a normal dog, for the diuresis continued in such manner that the total urine for the 24 hours was increased. In other words, the secondary oliguria (which occurs in non-diabetic animals, during the latter part of the glycosuria, in consequence of the blood-sugar having become combined) is absent in a diabetic animal. Moreover, there is a great increase of nitrogen elimination; and this increase, together with the polyuria, persists even two days after the injection. It is not difficult to figure that the surplus excretion of sugar (that is, the quantity in excess of the previous average) caused by the injection exceeds the quantity of injected sugar.

December 30, there was a subcutaneous injection of 3 g. dextrose per kilo. The result was moderate diuresis and increase of nitrogen. The surplus excretion of sugar was apparently greater than the quantity injected. The results as respects diuresis and nitrogen were not so great as after the preceding

DOG 20.

Diet 500g. Meat.
Water 100cc. at 9 A.M. & 4.30 P.M. by tube.

Date	Hour	Treatment	Urine Quant. cc.	Urine Sugar %	Nitro. g.
Dec. 20	9 A.M.		190	Heavy	
" 21	9 A.M. 5 P.M.		330 28	Mod. slight	
" 22	9 A.M. 5 P.M.		294 132	2.08 0	
" 23	9 A.M. 5 P.M.		220 154	0.8 5.2	
" 24	9 A.M. 5 P.M.		210 50	1. 2.6	
" 25	9 A.M. 5 P.M.		326 118	0.8 1.33	
" 26	9 A.M. 5 P.M.		250 (Total 24 hours 368) 95	0.2 6.	13.86
" 27	9 A.M. 5 P.M.	Intravenous injection of 20.4cc. 80% dextrose solution (3g. per kilo).	256 (Total 24 hours 351) 288	1. 4.8	13.67
" 28	9 A.M. 5 P.M.		310 (Total 24 hours 598) 150	5.6 6.	18.35
" 29	9 A.M. 5 P.M.		250 (Total 24 hours 410) 206	1.7 3.5	17.91 3.54
" 30	9 A.M. 5 P.M.	Subcut. injection of 21cc. 80% dextrose solution (3g. per kilo).	210 260	4.9 11.2	8.88 5.43
" 31	9 A.M. 5 P.M.		200 140	9.1 10.4	9.52 4.155
Jan. 1	9 A.M. 5 P.M.		175 260	3.2 6.	8.87 7.4
" 2	9 A.M. 5 P.M.		160 270	1.6 6.	7.1 7.
" 3	9 A.M. 5 P.M.	Subcut. injection of 22cc. 80% saccharose solution (3g. per kilo).	144 245	1.6 5.	5.03 4.27
" 4	9 A.M. 5 P.M.		300 230	6. 6.63	10.63 7.5
" 5	9 A.M. 5 P.M.		290 320	5.21 5.	12.59 7.28
" 6	9 A.M. 5 P.M.		220 285	5. 10.4	8.81
" 7	9 A.M. 5 P.M.		226 290	11.3 11.2	
" 8	9 A.M.		340	12.	

intravenous injection. This is natural. An intravenous injection should naturally be somewhat more effective than a subcutaneous injection. Moreover, let it be noted that the diuresis occurred on a *fixed* quantity of water intake, when the dog was *very thirsty*. If the dog had been allowed to drink freely, as many non-diabetic dogs were allowed to do after injection, the diuresis would have been much greater. But a true diuretic should be able to dry the tissues in this manner.

January 3, there was a subcutaneous injection of 3 g. saccharose per kilo. The result was a diminution of the evening urine, as compared with the several days preceding, and a diminution of the evening nitrogen. Elimination of the retained water and nitrogen occurred the following morning. The alteration in diuretic activity is apparently specific for dextrose. Saccharose injected subcutaneously in a diabetic animal has the same mild anti-diuretic effect frequently seen in non-diabetic animals.

DOG 64.

Starvation from June 16 to June 25.
Water 200cc. at 9 A.M. & 5 P.M. by tube.

Date	Hour	Treatment	Urine		
			Quant. cc.	Sugar %	Nitrogen g.
June 19	9 A.M.		160	-	
	5 P.M.		110	-	0.85
" 20	9 A.M.	Subcut. injection of 500cc. 0.85% NaCl. solution.	110	-	0.83
	1 P.M.		80	-	
	2 P.M.		8	-	
	5 P.M.		13	-	0.54*
" 21	9 A.M.		360	-	1.47
	1 P.M.		143	-	
	5 P.M.		100	-	0.695
" 22	9 A.M.		200	-	0.99
	1 P.M.		160	-	
	5 P.M.		40	-	0.69
" 23	9 A.M.	Subcut. injection of 500cc. 5% dextrose solution.	235	-	1.2
	1 P.M.		90	4%	
	5 P.M.		30	4.2%	1.27
" 24	9 A.M.		570	0.27%	3.4
	1 P.M.		155	faint	
	5 P.M.		60	-	0.81
" 25	9 A.M.		225	-	1.1
	5 P.M.		130	-	

*Afternoon nitrogen always represents total of urine since 9 A.M.

Summary for Dog 64.

The dog was diabetic since June 7, and in good condition.

June 20, there was a subcutaneous injection of 500 cc. saline solution. The diuresis was somewhat less prompt than usual.

June 23, there was a subcutaneous injection of 500 cc. 5 per cent dextrose solution. The result was interesting. The urine contained above 4 per cent sugar, yet the evening specimen was only 19 cc. more than on June 20. Active diuresis was not evident till the next day. The total sugar excreted was far less than that injected.

Remark. — It is the accepted opinion among those who believe in an internal secretion of the pancreas, that this substance is actively and rapidly used up in metabolism. It is not like a ferment, which may continue to work on its substrate for a considerable period, and is even protected from deterioration by the presence of its substrate. So active is the consumption of pancreatic amboceptor, that the effects of pancreas-extirpation are quickly evident, and within a very few hours after the operation, the organism which before was abundantly stocked with amboceptor, has become bankrupt; and the appearance of free sugar and other signs reveal the frank diabetes. In some manner, overstrain of the assimilative powers affects the organism injuriously in diabetes.*

On the other hand, it is well known, that if a patient has a certain power of utilizing dextrose, this power can be increased by suitable diet which checks the glycosuria. In other words, when the strain upon the assimilative power is relieved, when the sugar-ingestion is brought below the quantity that can be utilized, the pancreas proceeds to "catch up" with its work. The absence of hyperglycemia is proof that the pancreas is equal to its load. Then, the surplus amboceptor is stored in the reservoirs of the tissues, till finally a considerable supply may be accumulated where formerly there was none. Accordingly, the

* Since the injurious effect of giving dextrose (causing a surplus excretion of dextrose above the dose administered, together with breaking down of body protein, and increased excretion of nitrogen) is seen even in totally depancreatized dogs, which have no pancreatic tissue and no amboceptor for dextrose, this injurious effect of sugar is evidently exerted not entirely upon the pancreas nor upon the amboceptor, but upon other organs, possibly upon the liver, and probably through the nervous system. The effect is thus somewhat analogous to the increased glycosuria which may be caused in completely depancreatized dogs by adrenalin or piqure, and doubtless also by salt injections.

assimilative power is now improved, and carbohydrate may be tolerated in doses that formerly caused glycosuria. This conception is in accord with the facts known for human patients, and with several other observations upon animals in the course of the present research.

This fasting diabetic dog, in the mild early stage of the disease, had been free from glycosuria for several days. This meant that the pancreas was superior to its burden, and a small stock of amboceptor was accumulating. Therefore, on June 23, the injection of a moderate dose of sugar did not cause the intense polyuria, and the excretion of more sugar than that injected, as it does in an animal with active glycosuria. There was indeed a little diuresis as compared with the saline control, because the animal was diabetic and its accumulated stock of amboceptor very small. But the principal diuresis was secondary, and a considerable proportion of the injected sugar was burned, because there was actually some amboceptor present to bind the sugar in some degree.

Summary.

July 7, the injection of 500 cc. 5 per cent dextrose was repeated, the dog being now on regular diet. Notice should be taken of the difference between this experiment and the results of the same dose on June 23, when the dog was fasting and had a small stock of amboceptor. In today's experiment, the dog was already glycosuric, *i.e.*, bankrupt in amboceptor. Therefore, the introduction of this additional quantity of crystalloid dextrose caused a profuse diuresis, with excretion of a surplus of sugar greater than the dose injected, the extra sugar being derived from protein, as indicated by the greatly increased nitrogen excretion.

July 12, there was a subcutaneous injection of 500 cc. saline solution. The result was diuresis, very much as in a normal dog; but nothing like the profuse polyuria following the sugar injection.

July 16, there was a subcutaneous injection of 5 g. dextrose per kilo, in 80 per cent solution. In spite of the usual bullæ of œdema at the injection site, and the dog's thirst, the result was diuresis; and the 1 p.m. specimen, containing more sugar than the 5 p.m. specimen, was also greater in volume.

July 22, the same subcutaneous injection (5 g. per kilo in 80 per cent solution) was repeated, this time with a full supply of

DOG 64.

Diet 350g. Meat.
Water 750cc. per day by tube.

Date	Hour	Treatment	Urine		
			Quant. cc.	Sugar %	Nitrogen g.
July 4	9 A.M.		400	2.9	
	5 P.M.		275	3.65	
" 5	9 A.M.		525	1.4	
	5 P.M.		341	2.8	
" 6	9 A.M.		230	2.	
	1 P.M.		80	3.3	
	5 P.M.		125	7.3	2.79*
" 7	9 A.M.	Subcut.injection of 500cc. 5% dextrose solution.	320	4.5	6.7
	1 P.M.		225	7.3	
	2 P.M.		90	7.3	
	5 P.M.		260	7.3	5.325
" 8	9 A.M.		585	3.6	8.44
	5 P.M.		485	4.3	6.1
" 9	9 A.M.		305	4.3	5.48
	5 P.M.		405	4.	4.47
" 10	9 A.M.		325	4.1	6.63
	1 P.M.		55	2.	
	5 P.M.		105	2.4	1.91
" 11	9 A.M.		470	2.6	6.86
	1 P.M.		185	7.4	
	5 P.M.		115	5.	4.73
" 12	9 A.M.	Subcut.injection of 500cc. 0.85% NaCl solution.	250	6.	5.89
	1 P.M.		160	6.	
	5 P.M.		160	7.2	4.86
" 13	9 A.M.		305	5.2	6.83
	1 P.M.		360	4.5	
	5 P.M.		195	5.2	5.77
" 14	9 A.M.	Diet increased to 500g. meat daily.	350	4.5	6.5
	1 P.M.		177	1.5	
	5 P.M.		125	1.2	3.91
" 15	9 A.M.		850	5.2	9.39
	1 P.M.		185	5.6	
	5 P.M.		215	5.2	
" 16	9 A.M.	Subcut.injection of 43.75cc. 80% dextrose solution (5g. per kilo).	470	4.6	
	1 P.M.		240	7.3	
	5 P.M.		190	6.6	
" 17	9 A.M.		425	7.3	
	1 P.M.		200	4.3	
	5 P.M.		180	4.1	
" 18	9 A.M.	Diet changed from horse-meat to beef (500g).	465	5.2	
	1 P.M.		115	5.2	
	5 P.M.		155	7.3	

DOG 64 (Continued).

Date	Hour	Treatment	Water	Urine		
				Quant. cc.	Sugar %	Nitrogen g.
July 19	9 A.M.	Measured water begun, ad libitum.		450	5.3	
	1 P.M.		500	175	6.6	
	5 P.M.			265	4.5	
	8 P.M.		410			
" 20	9 A.M.		25	575	3.6	
	1 P.M.			150	6.	
	5 P.M.		275	200	7.1	4.1*
" 21	9 A.M.		530	535	5.4	9.28
	1 P.M.		80	125	4.5	
	5 P.M.		285	250	5.1	4.95
" 22	9 A.M.	Subcut.injection of 43.75cc. 80% dextrose solution (5g.per kilo).	230	480	4.3	8.33
	1 P.M.		594	355	6.6	
	5 P.M.		445	360	5.6	6.02
" 23	9 A.M.		600	600	4.	9.27
	1 P.M.		125	178	5.	
	5 P.M.		315	315	5.2	6.6
" 24	9 A.M.		400	615	4.3	10.5
	1 P.M.		200	250	4.4	
	5 P.M.		410	450	4.5	7.11
" 25	9 A.M.		220	505	4.5	9.37
	1 P.M.		280	215	5.2	
	5 P.M.		310	325	5.2	4.36
" 26	9 A.M.		320	475	6.	9.16
	1 P.M.		130	110	4.9	
	5 P.M.		185	170	5.	4.41
" 27	9 A.M.	Subcut.injection of 21g. 80% levulose solution (3g. per kilo).	190	280	4.1	5.43
	1 P.M.		520	245	6.1	
	5 P.M.		270	210	5.6	5.32
" 28	9 A.M.		590	500	5.2	8.62
	1 P.M.		115	120	3.8	
	5 P.M.		135	175	3.6	5.33
" 29	9 A.M.		435	820	4.05	13.28
	1 P.M.		160	155	5.2	
	5 P.M.		290	240	5.2	6.41
" 30	9 A.M.		305	465	5.	11.01
	1 P.M.		0	55	4.3	
	5 P.M.		160	80	4.9	2.92
" 31	9 A.M.		250	345	6.	8.56
	1 P.M.			125	5.2	
	5 P.M.		280	115	5.2	4.795
Aug. 1	9 A.M.		400	340	7.3	8.85
	1 P.M.			85	5.2	
	5 P.M.		240	80	9.1	3.48

*Afternoon nitrogen always represents total for urine since 9 A.M.

DOG 64 (Continued).

Date	Hour	Treatment	Water	Urine		
				Quant. cc.	Sugar %	Nitrogen g.
Aug. 2	9 A.M.		490	390	7.3	9.12
	1 P.M.			160	3.6	
	5 P.M.		350	175	6.6	5.85
" 3	9 A.M.	Subcut. injection of 35g. lactose in 50% solution (5g.per kilo).	180	325	4.3	7.41
	1 P.M.		385	120	8.1 (as dextrose)	
	5 P.M.		270	185	9.6 (as dextrose)	3.68
" 4	9 A.M.		440	600	6.	9.94
	1 P.M.		220	205	6.3	
	5 P.M.		130	155	5.9	5.81
" 5	9 A.M.		500	700	5.2	11.62
	1 P.M.			125	4.8	
	5 P.M.		525	355	4.9	6.25
" 6	9 A.M.		225	395	5.2	8.78
	1 P.M.		135	85	6.4	
	5 P.M.		220	230	8.1	4.89
" 7	9 A.M.		130	285	4.5	7.68
	1 P.M.			145	6.	
	5 P.M.		290	120	7.3	4.24
" 8	9 A.M.		250	375	3.6	6.15
	9.45 "	Intravenous injection of 100cc. 30% dextrose solution.		12	0	
	11 A.M.			365	4.9	
	12 M.			90	5.6	
	1 P.M.		550	70	6.1	
	3.30 "			130	5.2	
	5 P.M.		250	30	5.6	3.39
" 9	9 A.M.		340	375	5.2	8.625
	1 P.M.			150	6.	
	5 P.M.		400	200	6.	5.01
" 10	9 A.M.		300	420	4.05	9.38
	1 P.M.		120	110	4.9	
	5 P.M.		180	200	5.6	4.12
" 11	9 A.M.	Not fed today.	265	310	4.1	7.725
	1 P.M.		50	25	1.7	
	5 P.M.		40	40	0.4	0.84
" 12	9 A.M.	Not fed today. 100cc. solution containing 70g. dextrose (10g. per kilo) by stomach tube.	20	50	faint	1.01
	1 P.M.		840	300	7.3	
	5 P.M.		145	710	3.7	1.3
" 13	9 A.M.	Not fed.	70	32	1.8	0.42
	1 P.M.			7.5		
	5 P.M.		70	8.5	5.9	0.22
" 14	9 A.M.	Not fed.	30	55	faint	0.97
	1 P.M.		15	9	-	

drinking-water. Non-diabetic dogs under these conditions show diminished urine, as has been noted. The tremendous polyuria in this diabetic dog is a striking contrast. As usual, the breaking down of protein was indicated by the increased nitrogen excretion.

July 27, there was a subcutaneous injection of 3 g. levulose per kilo. The dog's drinking was greatly increased, and the urine was not increased in proportion. The output of both water and nitrogen was fluctuating at this time, so that accurate judgment is difficult. Also, the possibility is not excluded, that a tendency to diuresis may result from conversion of part of the levulose into dextrose. But it seems probable that the action of levulose itself was anti-diuretic, just as in a normal dog. The retention of water was proved by the sudden and great increase of weight, and by the secondary polyuria which occurred during the night of July 28–29, with corresponding drop in weight. The conditions here are obviously complex, and it is regretted that there has been no opportunity for a closer study.

August 3, there was a subcutaneous injection of 5 g. lactose per kilo. The result was diminished urine and diminished nitrogen on that evening, just as sometimes occurs with normal dogs. No attempt was made to calculate the excreted lactose separately from the dextrose. But the figures show that lactose has not the effect upon the animal that dextrose has. The increase of dextrose excretion, and the great increase of nitrogen, are lacking.

The results with saccharose (Dog. 20, January 3), and with levulose and lactose in the present dog, seem to indicate that the action of dextrose in diabetic animals is specific. Distemper and extraneous difficulties have spoiled other experiments undertaken along these lines.

August 8, this same dog received an intravenous injection of 100 cc. 30 per cent dextrose solution [compare with the intravenous injections in Dog 21 on August 4 and August 11, page 325]. It will be observed that dextrose is a diuretic throughout. There is no secondary oliguria. A really absolute parallelism between glycosuria and diuresis is of course impossible; nobody should wish to maintain that sugar is the only factor governing the diuresis. Loss of water and renal injury are both factors to be considered. But it is to be noted that these factors do not suffice to produce in diabetic animals the secondary oliguria observed in non-diabetic animals after intravenous injection of dextrose.

August 12, the dog, now fasting, received 10 g. dextrose per kilo by stomach-tube. The enormous polyuria is obvious, especially as compared with the preceding 24 hours. The increase of nitrogen is not so marked, probably because by this time the dog had become seriously weakened.

The following dog was not a very strong animal to start with. By June 15 weakness was well-marked, and was greatly increased by the large dextrose injection. The animal was practically dying when chloroformed on June 16. No infection was found at autopsy.

DOG 65.

Water ad libitum, measured.

te	Hour	Treatment	Water cc.	Urine		
				Quant. cc.	Sugar %	Nitrogen g.
ne 13		Total removal of pancreas.				
14	10.30 A.M.			100	6.1	2.28
	4.30 P.M.		475	185	1.8	1.7
15	10.30 A.M.	Subcut. injection of 60cc. 80% dextrose solution (10g. per kilo).	165	220	3.6	2.7
	11 A.M.		38			
	12 M.		90	65	5.2	
	1 P.M.		90	35	9.1	
	2 P.M.		70	40	9.1	
	3 P.M.		37	25	9.1	
	4 P.M.		100	30	9.1	
	5 P.M.		70	25	7.3	1.1*
16	10.30 A.M.		450	350	7.3	1.73
	1 P.M.		0	85	7.3	0.65
	3 P.M.	Chloroformed.				

tal of specimens since 10.30 A.M.

Summary for Dog 65.

The result might have been better in a stronger dog. Even in this dog, the diuresis for 24 hours following the injection was positive, and the character of the urine was light and pale, as contrasted with the dark, heavy urine after injection in non-diabetic dogs.

Even in a strong dog, however, the diuretic effect of dextrose will be found the same, whether the pancreas is completely or incompletely removed, provided that the partial removal has caused severe diabetes. The very existence of the characteristic diabetic glycosuria and polyuria means that the supply of ambo-

ceptor has given out; that the pancreas remnant, if there is one, is behind in its work, so that the tissues have used up the available supply, and dextrose has appeared in the circulation in uncombined form. Under these conditions, all dextrose that may be introduced remains uncombined. Therefore from the standpoint of diuresis, it is immaterial whether the entire pancreas has been removed, or whether an inadequate fragment remains. The subject will be more fully discussed in the next chapter.

DOG 38.

Water ad libitum.

Date	Hour	Treatment	Urine	
			Quant. cc.	Sugar %
Aug. 20	9.15 A.M. 5 P.M.	Diet 400g. lean beef.	270 100	- -
" 21	9.15 A.M. 5 P.M.		120 240	- -
" 22	9.15 A.M. 5 P.M.	Subcut. injection of 15g. dextrose in 80% solution (3g. per kilo).	185 68	- -
" 23	9.15 A.M. 5 P.M.		200 175	- -
" 24	9.15 A.M. 5 P.M.	Fed 400g. bread-and-meat mixture instead of usual meat.	175 165	- 3.6
" 25	9.15 A.M. 5 P.M.	Diet of 250g.bread-and-meat mixture begun.	340 185	4.5 6.1
" 26	9.15 A.M. 5 P.M.		280 230	5.2 6.1
" 27	9.15 A.M. 5 P.M.		290 370	5.6 7.3
" 28	9.15 A.M. 5 P.M.	Subcut. injection of 15g. dextrose in 80% solution.	215 375	5.1 12.2
" 29	9.15 A.M. 5 P.M.		270 485	3.2 5.6
" 30	9.15 A.M. 5 P.M.		135 440	5 7.3
" 21	9.15 A.M. 5 P.M.	Not fed today.	160 45	5.6

Summary for Dog 38.

On August 2, nearly seven-eighths of the pancreas had been removed, leaving the duct undisturbed. Digestion remained excellent.

This dog offers an example of the condition which I shall call *diabetes levis*. That is, on meat diet she is free from glycosuria, but on bread (or bread-and-meat) diet there is abundant glycosuria. For particulars see Chapter X. These dogs have a supply of amboceptor, for they thrive for long periods, even on the diet which keeps them glycosuric; and much of the carbohydrate of their food is utilized. Sugar is evidently to some extent diuretic for them, for the urine is more abundant on carbohydrate than on non-carbohydrate diet. The increase of polyuria from August 24 to 30, as the diabetes was aggravated by the diet, may also be noted. Nevertheless the great polyuria of the severely diabetic dogs is never present. Studies of the diuresis in such animals are calculated to throw light upon conditions regarding amboceptors, but, for reasons mentioned above, I have been able to perform tests only in this one dog.

August 22, on meat diet and with urine free from sugar, the dog received a subcutaneous injection of 3 g. dextrose per kilo. No glycosuria resulted, and the evening urine was diminished, just as in a normal animal.

August 28, on a diet of bread-and-meat mixture, with the urine averaging 5 or 6 per cent sugar, the same dose was repeated. The result was diuresis, but very slight in proportion to the marked increase in the sugar percentage, and in proportion to what occurs in dogs with severe diabetes. The record may be interpreted to mean that the entire dose of injected sugar was excreted.

The condition of these dogs may be explained on the principles heretofore stated. The amount of pancreatic amboceptor is greatly diminished, but yet enough is always present to prevent the fatal type of diabetes (*diabetes gravis*). The excess of circulating dextrose is very poorly combined; the proportion of sugar to amboceptor in the complex is high. The tissues can use it, but much more slowly and difficultly than normal. On meat diet, without glycosuria, there is a better supply of amboceptor, and dextrose acts as an anti-diuretic. On bread diet, with glycosuria, there is little amboceptor available. Portions at least of the sugar are so loosely combined that their effect upon the kidney

begins to approach that of a crystalloid; but yet the intense diuretic action of actually uncombined dextrose is never seen. If these observations are confirmed, an explanation other than the above may be rendered difficult. For these dogs on bread diet are as heavily glycosuric as dogs with *diabetes gravis* on meat diet; also the injected dextrose is excreted quantitatively or almost so. The diuretic differences between these dogs and dogs with *diabetes gravis*, easily explained on the basis suggested above, may not be so easy to explain on other hypotheses.

C. Interpretation of Experiments.

For convenience, the effects of injections of different sugars in doses up to 5 g. per kilo, in Dogs 21 and 18 (normal), are expressed in the following tables. The figures in the columns denote cc. of urine, taken from the records already presented. The injection day is denoted by a figure at the left, indicating the number of grams per kilo injected. The preceding and following days are those preceding and following the injection in the animal's record. The upper and lower figures of each day denote the morning and evening urine respectively. The comparative effects of the same dose of different sugars upon the volume of urine is thus clearly indicated.

Diuretic Effects of Subcutaneous Injections.
Table 1. lg. doses.

	DOG 21				DOG 18	
	Dextrose	Levulose	Galactose	Lactose	Maltose	Saccharose
	250	260	345			390 245
	350 230	260 194	360 230	205 252	140 120	194 165
	330 270	170 170	290 280	405 190	160 339	200 140
lg.	270 205	230 147	280 225	265 228	400 200	245 215
	345 240	220 265	270 280	270 323	260 230	210 278
	580 220	225 185	350 220	310 230	385 175	295
	330	330	360	310	255	410 (24 hours)

Diuretic Effects of Subcutaneous Injections.
Table 2. 2g. doses.

	DOG 21.	
	Dextrose	Levulose
	240	265
	580	225
	220	185
2g.	330	330
	180	170
	180	290
	313	240
	425	330
	210	180
2g.	330	
	100	
	230	
	260	
	280	
	235	
	260	

Diuretic Effects of Subcutaneous Injections.
Table 3. 3g. doses.

	DOG 21				DOG 18	
	Dextrose	Levulose	Galactose	Lactose	Maltose	Saccharose
	280	330	270	310	385	295
	235	180	280	230	175	
	260	340	350	310	255	* 410
	275	180	220	185	173	206
3g.	260	415	360	350	265	210
	175	124	205	257	140	227
	360	250	205	175	180	135
	245	300	252	315	206	155
	450	330	405	295	240	275
	220	180	190	218	298	227
	290	220	255	320	300	360

*24 hour specimen.

Diuretic Effects of Subcutaneous Injections.
Table 4. 4g. doses.

	DOG 21.	
	Dextrose	Levulose
	245	300
	450	330
	220	180
4g.	290	220
	120	162
	275	160
	330	180
	400	400
	240	220
	362	335
	230	210
	320	320

Diuretic Effects of Subcutaneous Injections.
Table 5. 5g. doses.

	DOG 21			DOG 18		
	Dextrose	Levulose	Lactose	Maltose	Saccharose	Saccharose
	400 240	400 220				
	362 230	335 210	295 218	180 206	275 227	255 265
	320 230	320 230	320 240	240 298	360 195	225 165
5g.	275 95	275 89	365 267	300 118	300 210	290 290
	280 350	290 345	325 340	280 180	165	140 120
	420 260	360 230	300 227	320 240		160 339
	260 194	290 280	265 220	380		400
	170 170	280	230			
	230					

The tables, and the numerous similar results not tabulated, seem to me to be explainable on the basis of colloid combinations and no other. Differences in specific diuretic action of different sugars upon the kidney may be thought of, but no such differences can be demonstrated by intravenous injection; differences, for example, such as those seen here between maltose on the one hand and saccharose and lactose on the other, or between dextrose and levulose on the one hand and galactose on the other. Differences in the percentage of sugar that passes into the urine cannot explain, for levulose appears in the urine in very high percentage, yet inhibits diuresis fully as powerfully as dextrose. Differences in the rate of diffusion and absorption, or differences in the quantity of fluid that collects at the site of injection, do not exist in any such ratio as these differences in diuresis. For example, the absorption of lactose is known to be slow, yet it and saccharose come the nearest to being diuretics. Neither does any dividing line here exist between monosaccharides and disaccharides.

The one and only distinction is very simple. The assimilable sugars inhibit diuresis. The non-assimilable sugars have very little inhibitory effect. In other words, certain sugars can be brought into colloid combination, and are thus assimilated. Other sugars can be combined only very slightly, and are utilized very slightly. This may not be the only distinction regarding assimilation, for the protoplasm may have very slight power to split or burn lactose or saccharose, and may have less power to burn

galactose, for example, than dextrose. It is not unreasonable to suppose that amboceptor and ferment stand in some natural proportion; when the ferment exists the amboceptor also is present; when there is very little power to burn a given sugar, there is correspondingly little power to bind it. [The word *ferment* here refers to a power of the protoplasm, not to post-mortem happenings. Post mortem, there is no saccharase in the tissues. In life, they actually burn a little saccharose.] Different sugars combine with different amboceptors, and these amboceptors may be produced by different organs. Only the dextrose amboceptor comes entirely from the pancreas. The levulose amboceptor is presumably furnished by the liver. The liver perhaps furnishes most or all of the amboceptors for sugars other than dextrose. The different sugars are combined in different degrees of firmness. Their different effects upon diuresis are thus explained. Apparently no sugar (unless intravenously injected) circulates in an absolutely free state in the non-diabetic organism.

Lactose and Saccharose.

These two, relatively non-assimilable sugars may be considered first. The discussion concerns (1) their practical results as diuretics, and (2) the interpretation of their action.

1. *Practical Results as Diuretics.* — From the standpoint of the dropsical patient, these sugars are not genuine diuretics unless given intravenously. When given otherwise, their principal effect is to increase thirst. After subcutaneous injection, as has been noted, their effect is sometimes to diminish the evening urine a little, and sometimes to increase it a little. The effect in either direction is insignificant compared to the effect when given intravenously. But even when there appears to be a primary diuresis, it is invariably observable that the specimen which contains most lactose (or saccharose) is the smallest in volume. Also, after the lactose or saccharose is nearly or completely eliminated, there invariably occurs a secondary elimination of water greater than that during the period of sugar excretion. On this basis, a patient would be left in worse condition than before; for after the supposed diuretic is gone, he is left with more water to dispose of than if the sugar had not been given. The only exceptions to this rule were found with the largest doses, as 10 or 15 g. per kilo, which would never be used therapeutically. With such doses, it appeared as though the combining power of

the body for these sugars had perhaps been exceeded. The effect then was a primary polyuria followed by a secondary oliguria, viz., a behavior such as the same sugars show when given intravenously, and such as every true diuretic should show. But quantitatively, this diuresis is far less than after intravenous injection.

2. *Interpretation of the Action.* — The possibility that saccharose and lactose, introduced otherwise than intravenously, circulate in a poorly combined form, is suggested by the following evidence. First, the diuretic action is so different when they are given intravenously and when they are given subcutaneously. A certain percentage of lactose or saccharose in the urine as the result of subcutaneous introduction means little or no increase of urine; the same percentage in the urine as the result of intravenous introduction means profuse polyuria. Also, after subcutaneous injection, the specimen of urine containing the most sugar is the smallest in volume; after intravenous injection, the rule is the reverse. Second, the secondary polyuria, after the subcutaneously injected sugar has been eliminated, speaks for a combination. This secondary polyuria is one of the ear-marks of combined sugar. It does not result from free sugar. Thus, it is not found after intravenous injection of saccharose or lactose in any animal, nor after subcutaneous injection of dextrose in a diabetic animal. If subcutaneously injected saccharose and lactose circulate in free form, their diuretic action should resemble that of dextrose injected subcutaneously in a diabetic animal, that is, should be the same as after intravenous injection, aside from the time-interval necessary for absorption. Since the behavior of subcutaneously injected saccharose and lactose is different from the known behavior of free sugar, the conclusion is that subcutaneously injected saccharose and lactose probably circulate in loosely combined form. The conclusion is less strange when certain known properties of these sugars are considered, *e.g.*, their adsorption by proteins, and the jecorin-like combinations which they may form with lecithin.

The diuretic action of subcutaneously injected saccharose and lactose would then be explainable as follows. These sugars are so slightly combined with colloid that their anti-diuretic influence is small. But their osmotic power attracts water from the tissues. This surplus of water is what causes a primary diuresis, in the cases when it occurs after injection of these sugars. When the sugar is eliminated, and its slight anti-diuretic effect is thus re-

moved, the surplus water is eliminated more freely than before, hence the quantity of urine is greater than during the period of sugar-excretion. The free, intravenously injected sugar has a specific stimulating action on the renal cells; but the loosely combined sugar has a slight action in the other direction, owing to its slightly colloid character. The only diuresis that occurs after subcutaneous injection of saccharose or lactose is thus due not to the direct action of these sugars, but rather to the water which they attract from the tissues.

Other Sugars, Especially Dextrose.

The reader who has taken the trouble to follow this chapter carefully, has probably thought of some other explanations of the peculiar behavior of sugar, which seem easier than the assumption of a colloid combination of sugar. It is now time to review such possible hypotheses in detail.

We know that when sodium chloride, for example, is injected subcutaneously, its effect upon the urine is similar to its effect when injected intravenously, except for the time-interval necessary for absorption. The effect in either case is diuresis; and this diuresis naturally occurs during the time when the sodium chloride is circulating in the blood, not after the salt has been excreted. Now, when dextrose and other assimilable sugars are tried, a remarkable difference is encountered. For when given intravenously, these sugars are active diuretics. But when these sugars are given by any other route (oral, subcutaneous, intraperitoneal), the effect is exactly the opposite. They are absorbed, and they cause hyperglycemia, even in extreme degree; but all through this hyperglycemia, the urine is greatly diminished, and the higher the percentage of sugar in blood and urine, the smaller is the quantity of urine. Finally, after the sugar has entirely disappeared from the urine and the glycemia has returned to normal, diuresis begins, and all the water which was retained during the period of glycosuria pours out in a flood of polyuria. When any drug, such as hirudin, produces certain effects when given intravenously, and fails to produce those effects when given by any other way, it is universally assumed that this substance undergoes a change in the tissues, so that it does not reach the circulation in the same form as when given intravenously. Therefore, when sugar produces different and even opposite effects when given intravenously or through other channels, the

hypothesis here suggested is the same, viz., that it has undergone a change in the tissues. This view is strengthened by the fact that there is a condition, namely diabetes, in which dextrose behaves just like sodium chloride; that is, its effect is the same whether given intravenously or subcutaneously or by mouth, except for the time-interval necessary for absorption. The view is further strengthened by finding that other sugars do not show the same behavior in diabetes as dextrose, but continue to act in the diabetic animal just as in the non-diabetic. The hypothesis then is that dextrose in diabetes is present in its own crystalloid form, like the sugar which we inject intravenously; but that in normal animals, all sugar not injected intravenously reaches the circulation in combination with a colloid, which is derived from the pancreas, and which is called amboceptor because it binds the sugar in a form which can be anchored and utilized by the body-cells.

A pertinent question is where this union takes place. There is very little amboceptor in the blood at any given moment; and the unsuccessful attempts to treat diabetes with lymph indicate that the lymph and tissue-fluids are as poor in amboceptor as the blood. This substance presumably partakes of the nature of a sessile amboceptor; it is stored by the living cells of the body for use in their life-processes. Sugar enters the blood in combined form, when introduced orally, subcutaneously, or intraperitoneally. The one tissue that may be thought of as common to these three localities is the wall of the blood-capillary that absorbs the sugar. Excessively thin as this vessel-wall is, it is nevertheless a membrane known to possess wonderful properties in other respects. And among its properties is presumably that of absorbing various substances in a form in which they are suitable to enter the blood. The absorption of sugar is not a mere process of diffusion, but a vital action of cells, different sugars being absorbed at different rates. The capillary wall, although so thin, may be credited with the power of combining in colloid form the sugar which passes through its endothelial cells. The stock of amboceptor is presumably replenished from the small supply constantly carried by the blood. This idea is in harmony with known facts of transportation of materials in the blood; for example, the actual quantity of sugar in the normal blood is very small, yet the tissues are constantly using sugar very actively, and a very large total amount of sugar is transported by the blood daily. If the pan-

creas fails to keep up the supply of amboceptor, the stock runs short very quickly, as heretofore mentioned. In general therefore we may assume that all sugar which passes through a living membrane in a non-diabetic animal takes on a colloid form; and the most probable living membrane to effect the combination is the endothelial capillary wall.

Hypotheses opposed to this one, to account for the anti-diuretic action of dextrose in non-diabetic animals and its different effect in diabetic animals, may suggest themselves as follows:

I. Nervous influences.
II. Slow absorption.
III. Osmotic effects:
  (*a*) General.
  (*b*) Local.
IV. Higher dextrose percentages in diabetes.
V. Differences in cells rather than in sugar.

I. Nervous Influences.

It might be alleged—especially by those who deny the existence of any internal pancreatic secretion — that the nervous system of the diabetic is in some special condition, such that the reflex influence of sugar introduced into the alimentary canal or under the skin, or the presence of sugar in the blood, may by a nervous mechanism set up diuresis in the diabetic, although in the non-diabetic the effect is the opposite. This notion cannot be called plausible. There is no evidence in favor of it. Against it may be set down the simple facts of the case. Namely, sodium chloride behaves the same whether injected intravenously or otherwise, and in a diabetic or a non-diabetic animal. Sugars behave oppositely, according as they are introduced intravenously or otherwise. In diabetes, dextrose takes on a uniform behavior, like sodium chloride; whereas the other sugars continue to behave as in the normal animal. It will later be shown that conditions of the nervous system which simulate diabetes so far as glycosuria is concerned, do not show the diabetic behavior toward dextrose. The conclusion is that the hypothesis of specific nervous influences has no adequate foundation.

II. Slow Absorption.

In the frequent comparison between sugar and NaCl, it may be urged that NaCl is absorbed far more rapidly than sugar,

hence an earlier and more active diuretic action may be expected from it when given orally or subcutaneously, than when sugar is thus given. But the rate of absorption has nothing to do with the case. The point is that the sugar *is* absorbed, and hyperglycemia and glycosuria *are* produced. If sugar is a diuretic, it must cause diuresis during the period of hyperglycemia and glycosuria, not after all sugar has disappeared from blood and urine. Therefore the rate of absorption is immaterial. Allow whatever time is necessary for absorption; the fact is demonstrated that hyperglycemia and glycosuria *do* occur, and this period of hyperglycemia and glycosuria is precisely the period of oliguria. There is no evidence that diabetic animals, in which dextrose is a diuretic, absorb the sugar any more rapidly than non-diabetic animals. And different rates of absorption cannot be supposed to explain the different diuretic effects of dextrose, levulose, and maltose on the one hand, as opposed to galactose, lactose, and saccharose on the other.

III. Osmotic Effects.

Osmotic effects may seem to offer a plausible explanation; and these may be considered as general and local.

(*a*) *General Osmotic Effects.* — These include all disturbances caused by an injection everywhere except at the site of injection. Those specially to be thought of are general weakness, circulatory changes, and alterations of the kidney. The alterations of the kidney may be actual injury, perhaps with albuminuria, or a specific change in the permeability for sugar. Needless to say, such alleged changes fail to explain why all sugars have practically the same action when injected intravenously, but such opposite actions when introduced by other ways. The notion that failure of diuresis, in the presence of intense hyperglycemia and glycosuria, after large subcutaneous injections of sugar in non-diabetic animals, can be accounted for by the general weakness and depression, has already been answered by injecting large doses of sugar subcutaneously in diabetic dogs on the verge of death from extreme weakness, and observing diuresis in these animals. If circulatory changes are at fault, how can all sugars act alike when given intravenously, but oppositely when given subcutaneously? And why should these circulatory relations suffer change in diabetes with respect to dextrose, but not with respect to other sugars? Alleged renal changes are an equally inadequate explanation.

Renal changes should be at a maximum after large sudden intravenous injections, but these are the very ones that cause diuresis; and the polyuria occurs even in the presence of albuminuria. Renal changes cannot account for the fact that all sugars alike produce diuresis by intravenous injection, but by other modes of introduction show wide differences in behavior. Renal changes furthermore cannot explain the facts in diabetes, viz., that sugars injected intravenously behave as in normal animals, and injected subcutaneously behave as in normal animals, with the single exception of dextrose, the behavior of which subcutaneously here resembles the behavior intravenously. Therefore, none of the general osmotic effects of sugar injections explain the phenomena observed.

(*b*) *Local Osmotic Effects.* — A considerable collection of fluid at the site of injection will be obvious to anybody who gives a subcutaneous injection of a concentrated sugar solution. Even with a $7\frac{1}{2}$ per cent solution, Gumprecht observed the presence of fluid at autopsy, which sometimes consisted of unabsorbed sugar solution, but frequently contained no sugar, showing that the sugar had been absorbed before the liquid which its osmotic properties had caused to accumulate. It may be supposed that this local accumulation, by withdrawing water from the body, reduces the amount available for diuresis and thus diminishes the diuresis. Then, after the damaged local blood-vessels have had time to recover, and to absorb the extravasated liquid, this water is excreted by the kidneys and thus produces the secondary diuresis. Similarly, the osmotic action of sugar in the intestine causes excretion of water into the intestine, thus leading to diarrhea; and this loss of water accounts for the oliguria.

Various points may be considered with respect to this explanation.

First, if it explains anything, it at least does not explain away anything. The fact remains that dextrose introduced orally or subcutaneously is a diuretic in diabetes and an anti-diuretic in non-diabetes. The diabetic animal may show diarrhea from large doses of sugar by mouth; and the bullæ under the skin after subcutaneous injection of sugar in a diabetic animal are visibly and palpably the same as in a non-diabetic animal. Yet the diabetic animal shows diuresis from dextrose, even if the local osmotic effects are marked, and if the supply of drinking water is limited. The non-diabetic animal shows the anti-diuretic effect of dextrose,

even if water is supplied in abundance. An explanation based only upon local osmotic effects is, on this ground alone, inadequate.

Second, there is the action of sodium chloride. Anyone who injects a strong sodium chloride solution can easily see a large local accumulation of œdema-fluid. But the diuresis proceeds nevertheless. If sugar is the same diuretic whether given subcutaneously or intravenously, there is no reason why it should not behave like NaCl, that is, cause diuresis in spite of more or less local œdema.

Third, there is the different diuretic action of different sugars. Subcutaneous injections of dextrose, levulose, and galactose cause local accumulations of liquid which cannot be distinguished one from the other. Yet the effect upon the urine is very different. The explanation is not found in the percentages of sugar that pass into the urine, for, in small doses, dextrose fails to enter the urine at all, while levulose and galactose enter it in considerable and fairly equal percentage. Yet dextrose and levulose stand together as diminishing the urine markedly, while galactose diminishes it only slightly. Similarly, local accumulation of liquid is approximately the same after injection of lactose, saccharose, and maltose, yet maltose affects the urine very differently from lactose and saccharose.

Fourth, the effects of local œdematous accumulations may be tested experimentally. A series of such experiments was attempted with dextrin and glycogen, in diabetic and non-diabetic animals, with fixed water and with water ad libitum. Unfortunately, only three such experiments could be performed. (Dogs 34 and 19, pages 375, 376.)

The erythrodextrin and glycogen used were from Eimer and Amend. The dextrin causes a very large œdematous collection at the site of injection, the glycogen somewhat less. The œdema forms and disappears more slowly than with sugar. In the normal dog, water was limited, and the urine was accordingly diminished, especially on the morning after injection. In the diabetic dog, free drinking was permitted; the urine was not appreciably diminished after dextrin, and the diminution after glycogen was probably due to weakness. At any rate, the diabetic animal was as susceptible to the osmotic influence as the normal animal.

It is entirely reasonable to suppose that the subcutaneous injection of a substance possessing water-attracting properties but no diuretic activity, in an animal with a limited supply of water, will result at some stage in a diminution of urine. But it is not reasonable to suppose that an animal, with water standing in

front of it all the time, will allow its tissues to be dried out in this manner. On the contrary, we may expect the animal generally to drink enough to supply this osmotic demand and also keep up approximately normal diuresis. And it is particularly unreasonable to assume that the same rules will hold for a supposedly active diuretic like dextrose as for an inactive substance like dextrin. When dextrose enters the blood and the urine in enormous percentages, the diuretic effect should be manifested, even to the extent of drying the tissues somewhat. And when the animal is allowed to drink freely, it should drink enough to provide for its tissues and for the diuresis. In the diabetic animal, this is true. With a limited supply of water, subcutaneous injections of dextrose will cause diuresis at the expense of drying the tissues; and when water is freely supplied, the polyuria is still more profuse, and is not prevented by the accumulation of a certain amount of water under the skin. In the normal animal, glycosuria means oliguria, not because of the effect of sugar under the skin, but because of the effect of the colloid sugar circulating in the blood. Colloids injected intravenously diminish the output of urine. In other words, colloids introduced intravenously behave similarly to dextrose introduced orally or subcutaneously.

DOG 34 (Normal. Weight 6400g.)

Diet 225g. Bread-and-meat mixture, at 5 P. M.
Water 200cc. at 9 A.M. & 5 P.M. by tube.

Date	Hour	Treatment	Urine		
			Quant. cc.	Sugar %	Nitro. g.
Apr. 6	9 A.M.		365	-	3.68
	5 P.M.		250	-	1.12
" 7	9 A.M.	Subcut. injection of 100cc. 50% dextrin solution.	280	0	3.53
	1 P.M.		170		
	5 P.M.		50		
			(Total P.M. 220)	0.56	1.06
" 8	9 A.M.		150	1.3	4.
	5 P.M.		260	slight	1.31
" 9	9 A.M.		460	-	3.37
	5 P.M.		205	-	0.63
" 10	9 A.M.		390	-	3.84
	5 P.M.		160	-	0.92
" 11	9 A.M.		290	-	3.45

DOG 19 (Diabetic. Weight 5800g.)

Diet 700g. lean meat.
Water ad libitum, measured.

Date	Hour	Treatment	Water	Urine			Feces
				Quant. cc.	Sugar %	Nitro. g.	Nitro. g.
Mar. 29	9.15 A.M. 5 P.M. 9 P.M.		 160 125	1140	3.6		
" 30	9.15 A.M. 4 P.M. 5 P.M. 9 P.M.		200 275 15 200	800	3.	17.48	
" 31	9.15 A.M. 5 P.M.		350 560	1050	4.	16.99	
Apr. 1	9.15 A.M. 10.30 A.M. 5 P.M.	Subcut. injection of 25g. dextrin made up to 50cc. with distilled water.	600 575	1230	4.3	20.04	3.9
" 2	9.15 A.M. 5 P.M.		575 340	1125	4.4	19.77	6.26
" 3	9.15 A.M. 5 P.M.		400 575	1060	3.3	20.597	10.8
" 4	9.15 A.M. 5 P.M.		300 500	1030	3.	19.78	5.94
" 5	9.15 A.M. 5 P.M.		350 575	1020	2.4	19.94	1.078
" 6	9.15 A.M. 10.30 A.M. 5 P.M.	Subcut. injection of 25g. glycogen made up to 75cc. with distilled water.	500 460	1020 250	3.4 4.6	17.82	4.145
" 7	9.15 A.M. 5 P.M.		300 325	720 (Total 24 hrs 970). 450	4.8 4.	18.09	2.21
" 8	9.15 A.M. 5 P.M.		350	720 (Total 24 hrs 1170). 500	3.2 2.4	20.65	2.07
" 9	9.15 A.M.		675	600 (Total 24 hrs 1100).	2.4	19.15	2.95

IV. Higher Dextrose Percentages in Diabetes.

It may be supposed that the active diuretic effect of dextrose in diabetic animals is due to a higher concentration of the sugar in blood and urine than in normal animals, owing to the inability of diabetic animals to use it. Such an explanation would be open to the following objections.

(*a*) The alleged low percentage of dextrose in the blood of non-diabetic animals after subcutaneous injection is contrary to fact. For example, in Cat 171, a fasting animal, on June 14, after subcutaneous injection of 10 g. dextrose per kilo, the blood-sugar was found to be 0.585 per cent. In Cat 59, another fasting animal, after subcutaneous injection of 6 g. dextrose per kilo on two successive days, the blood-sugar was found to be 0.85 per cent. In Dog 34, a normal animal, on April 18, 30 minutes after intraperitoneal injection of 8 g. dextrose per kilo, the blood-sugar was found to be 0.43 per cent. In Cat 29 on October 15, after subcutaneous injection of nearly 12 g. dextrose per kilo, a test of the serum showed D = 0.624 per cent. In Dog 28 on March 14, after subcutaneous injection of 9 g. dextrose per kilo, the blood-sugar was 0.303 per cent. All the above animals were markedly oliguric, sometimes almost to anuria. The quantity of sugar excreted by all was very slight, though the *percentage* in the urine was generally high. In Dog 34 there was glycosuria up to 16.6 per cent, with nearly complete anuria. Dog 28, at the other extreme, had barely a trace of glycosuria. These animals may be contrasted with the diabetic Dog 19, which on March 16, without injection, had a blood-sugar of 0.326 per cent, and was passing every day about 800 cc. urine containing 2 to 7 per cent dextrose. But on March 6, when this animal had fasted for a few days, the blood contained only 0.158 per cent dextrose, and the urine only 0.54 per cent, and there was no polyuria. It is a general law, that the higher the hyperglycemia and glycosuria in a diabetic animal, the greater the volume of urine. It is a general law, that the higher the hyperglycemia and glycosuria in a non-diabetic animal, the smaller the volume of urine.

(*b*) Differences depending upon different concentrations of dextrose should be of degree, not of kind. Uniformly opposite effects, viz., diuresis in diabetic animals and anti-diuresis in non-diabetic animals, are not thus explainable. There should be some dose or some concentration in which dextrose shows at least some tendency to diminish the urine in diabetic animals, and some dose

or some concentration in which dextrose shows at least some tendency to increase the urine in non-diabetic animals. Inasmuch as these results are never obtained, the explanation based on concentration falls.

DOG 34 (Normal. Weight 6400g.)

Diet 225g. Bread-and-meat mixture.
Water 200cc. 9 A.M. & 5 P.M. by tube.

Date	Hour	Treatment	Urine		
			Quant. cc.	Sugar %	Nitro. g.
Mar. 30	9.30 A.M.		250	-	3.5
	1 P.M.		150	-	
	5 P.M.		50	-	0.89*
" 31	9.30 A.M.	Intravenous injection of 51.6cc. 25% dextrose solution (2g. per kilo).	250	-	3.865
	11 A.M.		170		
	12 M.		60	0.16	
	1 P.M.		25	slight	
	5 P.M.		58	faint	1.48
Apr. 1	9.30 A.M.		500	-	3.09
	11 A.M.		130	-	
	12 M.		6	-	
	1 P.M.		7	-	
	5 P.M.		33	-	0.9
" 2	9.30 A.M.		285	-	3.42
	1 P.M.		170	-	
	5 P.M.		34	-	1.09
" 3	9.30 A.M.		320	-	3.42
	1 P.M.		145	-	
	5 P.M.		20	-	0.97
" 4	9.30 A.M.	Subcut. injection of 130cc. 50% dextrose solution (10g. per kilo).	240	-	3.52
	10 A.M.		6	slight	
	10.30 A.M.		2	"	
	10.45 A.M.	Intravenous injection of 51.6cc. 25% dextrose solution (2g. per kilo).			
	11 A.M.		44	4.6	
	12 M.		16	3.8	
	1.30 P.M.		6	1.	
	5 P.M.		14	slight	0.25
" 5	7.30 A.M.		410	-	4.65
	1.30 P.M.		210	-	
	5 P.M.		70	-	1.14
" 6	9.30 A.M.		365	-	3.68
	5 P.M.		250	-	1.12
" 7	9.30 A.M.		280	-	3.53

*Afternoon nitrogen always represents total for urine after 9.30 A.M.

(*c*) The alleged importance of higher and lower percentages of dextrose in the blood may be tested experimentally. If this is the essential factor, then increase of the percentage of dextrose in the blood should increase the diuresis.

Here, on March 31, the intravenous injection of 2 g. dextrose per kilo resulted in the usual diuresis. On April 4, there was a subcutaneous injection of about 10 g. dextrose per kilo. An interval of an hour was then left, during which glycosuria and oliguria were present as usual. Then, the same intravenous injection was given as on March 31. The glycosuria of course proved that hyperglycemia existed before this injection, and of course fresh sugar was constantly being absorbed from the subcutis. Therefore, the intravenous injection today must cause greater hyperglycemia than on March 31. The net result of the experiment was *marked oliguria*. That is, the anti-diuretic effects of the subcutaneous sugar overcame the diuretic effects of the intravenous sugar.

It must be interesting that we are able thus to play off one form of sugar against the other, so that, after a double injection, though the hyperglycemia is higher, the diuresis is less. By varying the relative size of the doses injected subcutaneously and intravenously, the effects upon the urine can of course be varied. Such experiments tend to dispose of the idea that the difference between the diuretic effects of dextrose in non-diabetic and in diabetic animals is merely a matter of higher blood-sugar in the latter.

(*d*) The behavior of sugars other than dextrose throws light on the subject, especially as respects the influence of different quantities of sugar in the urine. The different monosaccharides and the different disaccharides cause approximately the same-sized bullæ of liquid at the site of injection, but the sugars themselves enter the urine in very different proportions. I have explained the different results on the basis that the organism not only burns some sugars less readily than others, but also combines them less readily. At any rate, the behavior of the different sugars offers an interesting comparison with diabetes; for the normal animal excretes lactose, for example, in practically quantitative fashion, just as the diabetic animal excretes dextrose. Other sugars show intermediate behavior.

Levulose, for example, when injected subcutaneously, inhibits diuresis as strongly as dextrose, yet passes into the urine in considerable percentage. Attention may again be directed to

the levulose experiments with Dog 21 [see table, pages 319 and 320]. On May 7, subcutaneous injection of 3 g. levulose per kilo diminished the evening urine, *although the levulosuria reached* 1.95 *per cent, and the dog was not thirsty.* On May 20, injection of 5 g. per kilo diminished the urine still more, although *the levulosuria reached* 5.2 *per cent.* Diarrhea remained absent, and the thirst was fully satisfied by the usual evening 200 cc. of water.

These and similar results would seem to rule out any argument that levulose really has a diuretic action after subcutaneous injection, but that the diuresis is prevented by the subcutaneous accumulation of water. That the subcutaneous accumulation of water after injection of only 3 g. levulose per kilo, should dry the body in such degree as to prevent diuresis from a levulosuria of 1.95 per cent, and yet the animal be not thirsty, is quite improbable. And after subcutaneous injection of 5 g. levulose per kilo, it was presumably not local œdema which caused the urine to diminish more than after injection of 3 g., although the levulosuria reached 5.2 per cent. Certainly no such anti-diuretic effects are obtainable from injections of dextrose in diabetic animals. The results with levulose merely obey the general law, that in normal animals, the more the sugar the less the volume of the urine, except after intravenous injection.

We pass next to lactose, the non-assimilable sugar. The experiments have shown that even if the urine of the 12 or 24 hours following subcutaneous injection is increased, the urine of the next 24 hours, after the lactose is eliminated, is more than during the period of lactosuria. Also, the more lactose a given specimen contains, the smaller generally is the volume of that urine. These results are opposite to the behavior of dextrose in diabetic dogs, and opposite to the behavior of intravenously injected lactose. On intravenous injection, the diuretic activity of dextrose and lactose is nearly equal; at least, nearly enough equal that Hedon and Arrous on one side debated with Lamy and Mayer on the other side as to which was the more active diuretic. The non-diabetic animal cannot utilize lactose, and the diabetic animal can utilize neither lactose nor dextrose. But dextrose subcutaneously injected in diabetic animals produces diuresis like that which follows intravenous injection; whereas lactose subcutaneously injected cannot produce such results in either non-diabetic or diabetic animals.

(*e*) The question is further illuminated by the effects of dextrose in partially depancreatized, non-diabetic animals. Attention is again called to the experiments with Dog 17 [see table, page 349]. These experiments and the others like them would seem decisive concerning the effects of dextrose. On March 24, the injection amounted to only 2 g. per kilo, and the dog was supplied freely with water. The glycosuria reached 1.2 per cent, and the urine was diminished. On March 27, injection of 6 g. per kilo led to a glycosuria of 5.6 per cent, and the urine was only a fraction of what should have resulted from the quantity of water which the dog drank.

It is beyond dispute, that if dextrose injected subcutaneously has any tendency to act as a diuretic, this tendency should be greater in an animal like the above, in which glycosuria occurs so easily, than in a normal animal, in which glycosuria does not result from these doses. But such tendency is entirely absent, and oliguria is the invariable rule, because dextrose circulates as a colloid.

(*f*) The behavior of animals with *diabetes levis* has been exemplified by Dog 38 (page 362). Here, there is abundant glycosuria on carbohydrate diet, and the subcutaneously injected dextrose seems to be quantitatively excreted. The dextrose causes some diuresis, because the animal is mildly diabetic. But the polyuria is not extreme, as in animals with *diabetes gravis*. It is relatively slight, presumably because the animal still possesses a small quantity of amboceptor. Explanation on any other hypothesis seems difficult.

(*g*) Later chapters will show that in certain forms of glycosuria, the amount of dextrose excreted after injection may be very large, even greater than the amount injected. But in these non-diabetic forms of glycosuria, dextrose is not an intense diuretic as in severe diabetes nor a mild diuretic as in mild diabetes, but is an anti-diuretic just as in normal animals.

V. Differences in Cells Rather than in Sugar.

It might be alleged that in diabetes the renal cells have become accustomed to excreting sugar, so that they dispose of it more efficiently, and excrete water in so doing. This and similar suppositions are ruled out by two facts. (*a*) The diuretic behavior of dextrose begins promptly with the beginning of diabetes, before there has been time for any training of the renal cells. (*b*) Normal

dogs — or more particularly, partially depancreatized non-diabetic dogs — can by sugar feeding be kept glycosuric for long periods. The latter animals, in particular, may be made to excrete sugar very freely. There is not the slightest tendency for dextrose to lose its anti-diuretic behavior in consequence of prolonged glycosuria.

I have not denied the influence sometimes exerted by changes in the permeability of the kidney. Some authors have sought to explain the greater ease with which dextrose passes the kidney in diabetes, by alterations in the cells of the kidney. Pflüger, for example, attributed the increased readiness of excretion to changes in the vital activity of the renal cells. De Meyer likewise has asserted that the sugar of the blood is free, but that the internal secretion of the pancreas acts upon the renal cells so as to make them impermeable for sugar; and he has attempted to support this opinion by the untrustworthy method of post-mortem experiments. It might be considered that this explanation accounts for the facts which I have presented concerning diuresis. The internal secretion of the pancreas is, according to my own statement, a substance which binds sugar to the cells. Also, according to my own statement, it partakes of the nature of a sessile amboceptor; that is, it is retained by the cells, and very little of it is present at any one time in the normal blood. Therefore, it may be supposed that this substance entangles the sugar, so to speak, and will not let it go. In this way, the body-cells are enabled to utilize the sugar thus bound to them. Likewise, the renal cells will not let the sugar pass through them into the urine. This action of the amboceptor may be expressed figuratively. The kidney without amboceptor may be like porous earthenware, freely permeable to both sugar and water. The pancreatic amboceptor may be to the renal cells as a deposit of copper ferrocyanide to the earthenware, transforming it into a semi-permeable membrane, allowing the water to pass but not the sugar. The osmotic properties of the sugar thus retained might then account for the diminution of urine. Also, from the standpoint of the tissues, the pancreatic amboceptor may be to the sugar as a mordant to a dye; it holds and fixes it. Under such conditions, the sugar in the blood may be entirely free, yet its behavior be governed by a pancreatic substance distributed to the renal and all other cells. This may seem a simpler and more reasonable hypothesis than the existence of sugar in combined form in the blood.

The figure which compares amboceptor and sugar to mordant and dye is one with which I am in sympathy. I believe also that most of the amboceptor of the body is anchored to the cells; and sugar approaching a cell probably encounters a denser stratum of amboceptor, and thus is firmly retained, and through increasingly firm colloid combinations is built up into the colloid protoplasm. But presumably there is a small amount of amboceptor in normal blood, and the sugar of the blood circulates normally in colloid form, because of the following fact.

When sugar in its own crystalloid form is introduced directly into the circulation, it runs through the renal filter just as easily as in diabetes, and with the same diuretic effect. But when it has to pass through a living membrane in order to reach the bloodstream, it undergoes combination and therefore acts as an antidiuretic.

The conclusion is that all the sugar of the normal body exists in combination with colloid pancreatic amboceptor.

Deficiency of this amboceptor is diabetes.

CHAPTER VII.

THE AMBOCEPTOR HYPOTHESIS.

Part I.

The subject of diabetes at present is so complicated and confused, that any hypothesis advanced to explain it must encounter a number of seeming contradictions. The first portion of this chapter will deal with the following matters, concerning which researches exist, that appear to offer more or less opposition to the doctrine of combined sugar.

1. Excretion and resorption in the normal kidney.
2. Relations between glycemia and glycosuria.
3. Intravenous injections.
4. Perfusion experiments.
5. Glycogen-formation in diabetes.
6. Avian diabetes.
7. Reptilian diabetes.
8. Ligations of the liver, and similar experiments.
9. Peculiarities of levulose.
10. The oat-cure.

The last two, namely levulose and the oat-cure, will be reserved for treatment in chapters by themselves. The others will now be considered in order.

1. Excretion and Resorption of Sugar in the Normal Kidney.

Theories and researches concerning the mechanism of urinary secretion cannot be treated here. But Nishi (3) has published experiments which seem to show excretion of sugar as a normal process in the glomeruli, and resorption in the tubules. Nishi's findings are as follows. In the kidney of mammals, sugar is present only in the cortex, while in the medulla there is normally no trace. In hyperglycemia without glycosuria there is increase of sugar in the cortex, but no sugar in the medulla. In diuretin and adrenalin glycosuria, the sugar-content of both portions of the kidney is high, but especially of the cortex. In phloridzin

glycosuria the kidney contains less sugar than in other glycosurias, and the medulla contains more than the cortex. In cases of adrenalin hyperglycemia without glycosuria, and sometimes in normal animals, perfusion under high pressure will force out a little sugar-containing fluid from the canals of the cortex, indicating that the urine in this portion, before passing through the length of the tubules, contains sugar. The (rabbit) kidney normally contains no glycogen; in hyperglycemia without glycosuria it contains a trace; in glycosuria it contains a small quantity. Nishi's opinion therefore is that the glomerular filtrate is normally, and especially in every hyperglycemia, sugar-laden, and through absorption in the canaliculi the urine becomes sugar-free before reaching the medulla.

If Nishi's conclusions be accepted, it might appear that they stand in favor of a free condition of the blood-sugar; that colloid sugar ought not to pass into the urine so readily. In this connection the question raised by Oppler may be important; the normal urine may contain no glucose. But leaving this aside, the fact is that colloids may enter the urine very readily. The normal blood certainly contains more sugar than dextrin, yet in normal urine there is a trace not only of reducing substance but also of dextrin. After injection of a little dextrin or foreign albumin into the circulation, these substances very readily pass into the urine. Therefore the fact that a trace of sugar passes into the urine does not prove that the sugar of the blood is a crystalloid.

2. Relations between Glycemia and Glycosuria.

Reference may be made to the facts concerning these relations outlined in Chapter I. The following may now be discussed:

A. Easy permeability of the non-diabetic kidney.
B. Difficult permeability of the non-diabetic kidney.
C. Easy permeability of the diabetic kidney.
D. Difficult permeability of the diabetic kidney.
E. Free sugar as a foreign substance.
F. The true test of permeability.

A. Easy Permeability of the Non-diabetic Kidney.

Glycosuria with normal blood-sugar is possible in conditions such as uranium poisoning and the rare "renal" glycosuria of

man. Lepine [(1), p. 209] and Lepine and Boulud (4) found glycosuria without hyperglycemia after injection of organ-extracts. Von Noorden [(3), p. 534] describes glycosuria in a normal person after ingestion of 200 g. dextrose, with blood-sugar of 0.1 per cent.

The possibility of changes in the permeability of the kidney, and the renal element in glycosuria, must be recognized. Most of the conditions above mentioned occur in connection with demonstrable renal injury. In von Noorden's patient it is incredible that glycosuria began with glycemia of 0.1 per cent; rather, it began when the blood-sugar was higher, and the analysis was taken on the down-slope. Frank has shown how glycosuria tends to continue under these conditions. The renal element suffices to explain all the slight variations of this sort found in non-diabetics. Lepine [(1), pp. 208–09] explains some such discrepancies on the basis of varying combinations of the blood-sugar. The suggestion is not impossible.

B. Difficult Permeability of the Non-diabetic Kidney.

Difficult permeability is normal and usual. Many authors have shown the high blood-sugar values frequently attained without glycosuria or polyuria. Accurate investigation will doubtless show that simple "alimentary" glycosuria is accompanied by oliguria. The normal impermeability of the kidney does not demonstrate the combined state of the blood-sugar, but it is more easily comprehensible on this assumption; and this consideration alone has been attractive enough to cause a number of authors to express their belief in a blood-sugar combination.

C. Easy Permeability of the Diabetic Kidney.

Loewit (3) found in depancreatized frogs that though hyperglycemia generally exists with glycosuria, the glycosuria may be present without hyperglycemia. Von Noorden [(3), p. 533] cites a human patient with diabetes of less than a year's standing, with glycosuria, yet in five tests the blood-sugar was only 0.109 per cent. Continuous, prolonged glycosuria in non-diabetic persons with normal kidneys and with blood-sugar as low as this is apparently impossible. The few reports of this nature may be interpreted somewhat in favor of the combined-sugar hypothesis.

D. Difficult Permeability of the Diabetic Kidney.

There is abundant evidence that glycosuria in diabetics is generally accompanied by hyperglycemia sufficient to cause glycosuria also in non-diabetics. Parallelism between glycosuria and hyperglycemia has been found by Pavy and by Gilbert and Baudouin, but the frequent striking discrepancies are shown in the figures of Liefmann and Stern and others. Falta's examples illustrate how the diabetic hyperglycemia may continue after the glycosuria (0.123 per cent blood-sugar 23 days after cessation of glycosuria; 0.21 per cent 9 days after cessation of glycosuria). Mohr described a depancreatized dog free from glycosuria for several days, with blood-sugar of 0.32 per cent. My Dog 19, on March 6, after several days of fasting, had a glycemia of 0.158 per cent, and the glycosuria was on the point of disappearing.

Totally depancreatized dogs and the severest human diabetics, in whom the blood-sugar may be considered uncombined, regularly excrete sugar apparently to the best of their ability, and the excretion is checked only by renal impermeability or systemic weakness. Mohr's dog was not completely depancreatized; the autopsy showed remnants of pancreatic tissue, and the important modifying effect of these is well known. Renal impermeability is one factor in the variations of diabetic glycosuria; von Noorden and Liefmann and Stern recognized that the older cases have higher blood-sugar in proportion to the glycosuria than the recent cases. This idea of acquired tolerance for sugar on the part of the kidney is not weakened by Frank's observation of a light case which turned severe over-night, and the plasma-sugar rose at once to 0.56 per cent. It is not necessary to assume here a sudden corresponding impairment of the kidney. As a matter of fact, the glycosuria was increased in proportion; the kidneys were evidently working to the best of their ability, but were overwhelmed by the flood of sugar. But in addition to the recognized renal element, the varying states of combination of the blood-sugar are important for explaining the discrepancies between glycemia and glycosuria. Figures like those of Liefmann and Stern become more easily comprehensible on this basis. Patients like those of Falta represent improvement spontaneously or under treatment; the supply of amboceptor is becoming more adequate; the blood-sugar is still poorly combined, therefore utilizable with difficulty, therefore the hyperglycemia; but the same sort of

combination which permits the combustion of the sugar also explains its retention by the kidney. All the facts harmonize with the doctrine of combined sugar.

E. Free Sugar as a Foreign Substance.

It may be supposed that if the normal blood-sugar is combined, then any trace of free sugar in the blood should be treated by the kidneys as a foreign crystalloid and quantitatively excreted; in some cases of diabetes there might thus even be hypoglycemia.

As a matter of fact, this assumed sensitiveness of the kidney to sugar is not necessarily correct. An interesting example is furnished by tortoises and selachians, whose normal blood may be considered absolutely or practically glucose-free. Yet the kidneys, especially of selachians, have a high impermeability for glucose, either from injection or in diabetes. It is also well known that sugar enters into loose physical or chemical relations with albumin, lecithin, and other substances; thus the sugar in the blood might be in the specific sense, from the standpoint of assimilation, free, and yet not be entirely free from the standpoint of the kidney. These non-specific linkings, if existent, are feeble; they do not avail to prevent glycosuria and polyuria when "free" sugar is in excess in the blood. But they may render it possible that bare traces of "free" sugar, like subliminal percentages of urea or salts, may fail to excite the kidney to activity.

The above may be a satisfactory explanation if any is needed, but probably none is needed. The fact is that in severe diabetes the kidneys seem to excrete sugar to the best of their ability. In other cases, the known relations between glycemia and glycosuria are readily explained by the varying renal permeability and the varying degrees of combination of the blood-sugar.

F. The True Test of Permeability.

In the above discussion, an existing misleading conception of permeability has been permitted to pass without question. The standard referred to has been merely the percentage of blood-sugar which causes the appearance of sugar in the urine in diabetic or non-diabetic cases. This standard affords no decision whether the blood-sugar is colloid or crystalloid. As previously mentioned, it is not true that traces of colloids pass into the urine less easily than traces of crystalloids; the dextrin in the urine normally and after injection of small quantities of dextrin is a sufficient exam-

ple. What is generally true is that crystalloids are excreted by the kidney with less effort and in larger quantities than colloids, and their effect upon the kidney is diuresis. On the other hand, colloids are excreted with greater effort and in smaller quantity; in large amounts they injure the kidney; their effect is oliguria. Among the above class of crystalloids undoubtedly belongs "free" glucose, as present after intravenous injection, or in diabetes. In the non-diabetic organism the behavior is the opposite. Give sugar to a diabetic, and the typical result, along with hyperglycemia, is glycosuria representing a considerable quantity of sugar, and polyuria. Give sugar to a non-diabetic sufficient to cause the same hyperglycemia as in the diabetic, and the result is the excretion of an insignificant quantity of sugar, with oliguria. Increase the dosage so as to increase the hyperglycemia, and thus attempt to force an excretion of sugar by the non-diabetic equal to that of the diabetic, and the result will be increased oliguria and, in the most extreme cases, albuminuria or anuria. The difference does not lie in a more efficient function of the diabetic kidney; on the contrary, authors have recognized that the diabetic kidney becomes less permeable, not more permeable. Give the sugar intravenously in large doses; the non-diabetic kidney shows no more injury than the diabetic; it excretes the sugar actively, with polyuria. These facts show the true distinction between crystalloid sugar and colloid sugar.

3. Intravenous Injections.

Sugar intravenously injected is largely utilized, so that more than half of it fails to appear in the urine. Since there is very little amboceptor in the blood, it may be inquired how this utilization of free, crystalloid sugar can take place.

The assumption throughout has been that the internal secretion of the pancreas has the character of a sessile amboceptor. It is chiefly anchored to the living cells, for use in their anabolic processes. Only a small quantity exists in the blood at any one time. The blood itself can bind very little sugar. A considerable fraction of the intravenously injected sugar reaches the kidney in free condition, and there acts as a diuretic and is excreted. But the kidney is only a small part of the entire circulation. All over the body, the sugar diffuses quickly through the walls of the capillaries into the tissue-spaces. It thus passes through a living membrane. It is changed and imprisoned, like a ray of light

passing through glass. In this membrane, or in contact with the tissue-cells, sugar becomes linked with amboceptor, and henceforth plays the part of colloid sugar. It is conceivable that an additional supply of amboceptor is also poured into the blood from the pancreas or from the tissue-reservoirs. At any rate, secondary oliguria soon sets in, even while the hyperglycemia is still great. The dextrose has become colloid, and as colloid it can be utilized. No such secondary oliguria occurs in a diabetic animal. When the intravenous doses are sufficiently small and slowly injected, so that they can be fully combined, there is oliguria from the outset, as Pavy demonstrated; and Pavy clearly recognized the colloid transformation of the sugar as the cause of the phenomenon.

This is a convenient place to enlarge upon the deposit of amboceptor in or about cells. A special affinity is here supposed between cells and amboceptor. Its distribution is therefore not equal. The blood-plasma contains only a little. The body-cells attract it from the plasma, as nerve-cells, for example, bind tetanus toxin. The cells or their immediate environment are therefore constantly loaded with it. It may constitute some of their so-called side-chains. Sugar is normally combined in the blood; but as it approaches a cell, it supposedly enters a denser stratum of amboceptor; it is therefore more firmly bound, is prevented from leaving the cell, and is built up through increasingly firm colloid combinations into the colloid protoplasm, or else is burned in the protoplasm. Some sort of relation probably exists between the concentration of amboceptor in the cells and in the plasma; in other words, a law of distribution. When the general supply of amboceptor is reduced, the supply in the cells is of course reduced, but the concentration in the cells is still far greater than in the plasma. Thus, a dog with *diabetes levis* (like Dog 38) or a patient with early mild diabetes, may show very poor combination of sugar in the blood, so that dextrose acts as a diuretic; yet there may be ability to utilize considerable dextrose. In more severe yet not "total" diabetes the sugar in the blood may seem to be absolutely free; the behavior may be entirely that of a crystalloid; and yet the patient may be able to burn a little sugar, because what trifle of amboceptor he has is quickly seized upon by the cells, hence is not found in appreciable amount in the blood, but is utilized by the cells in binding a little sugar for their consumption.

4. Perfusion Experiments.

Various authors, especially Grube (3), have proved that the liver can form glycogen from sugar in direct perfusion. McGuigan (4), also Hatcher and Wolf, proved that isolated limbs can utilize sugar in direct perfusion. Various researches, from that of Locke to the recent papers of Stewart and of Gayda, show that isolated organs such as the heart can make use of sugar. Therefore the question may be asked why taking these organs away from the pancreas should not lead to the same results as taking the pancreas away from the organs.

It is possible that the disturbance set up by the operation of pancreas extirpation, of itself accelerates certain changes in the liver or elsewhere, and hastens the onset of diabetes. But even so, the onset in mammals requires several hours, and in cold-blooded animals a day or two. It is not known how long isolated organs may retain their stock of amboceptor, but it is presumably as long as the time during which they are in other respects suitable for perfusion experiments.

It has been notoriously difficult to obtain a well-marked formation of glycogen in perfusion experiments. It is barely possible that the results might be improved by using naturally hyperglycemic blood. After a large subcutaneous injection of dextrose, there is great hyperglycemia, also active glycogen formation; the blood-sugar is combined as proved by the oliguria. If the blood of such an animal were used for perfusion, instead of blood to which sugar has been artificially added, it is conceivable that a better glycogen-formation might be obtainable; though there is also the possibility that the hypothetical blood-sugar compound may be broken up when the blood is shed.

Minkowski [(1), p. 94] mentions experiments of Lepine and Barral with perfusions of limbs of freshly killed dogs. Minkowski sets a low estimate upon the value of such experiments, on the ground that if the limbs of diabetic dogs utilize dextrose like the normal, the results are open to question as being due perhaps to post-mortem processes; and if the limbs of diabetic dogs are unable or less able than normal to utilize dextrose, the result is merely what has already been demonstrated in living diabetic animals. Nevertheless, it would seem desirable that such experiments should be repeated with the more recent and accurate methods of analysis. If limbs or organs of totally diabetic dogs

can burn dextrose as well as those of non-diabetic animals, the results of perfusion experiments in general will be called in question as post-mortem phenomena, for it will be evident that the tissues will be doing something post-mortem which they could not do during life. But the importance of positive results, the finding of demonstrable differences between diabetic and non-diabetic tissues in perfusion, should be very great. Such results would offer strong evidence, first that an internal secretion of the pancreas exists, and second that this internal secretion is stored in the tissues.

Since the above was written, Knowlton and Starling have published this very evidence. By suitable methods, they demonstrated sugar-consumption in the normal perfused dog-heart. This power is reduced to a minimum or disappears altogether when the heart and blood are from a depancreatized animal. Using diabetic blood, the sugar-consumption of the normal heart sinks. Perfusing a diabetic heart with normal blood restores the power of utilizing sugar. Also, boiled extract of pancreas added to diabetic blood enables the diabetic heart to utilize sugar. These experiments are therefore fully in accord with the conception concerning the internal secretion of the pancreas. The findings are also in accord with those of other authors, who have observed that formation of liver-glycogen or other functions are facilitated by use of pancreas-extract. In living animals, neither pancreas-extract nor normal blood confers the power of sugar-utilization, and even the largest quantities of diabetic blood do not impair the power of a normal animal to use dextrose (Hedon). The perfusion experiments, while interesting, cannot be accepted as conclusive proof until we know why the results differ from those obtainable in living animals.

5. Glycogen-Formation in Diabetes.

The diminished quantity of glycogen in the normal depots, and its presence in abnormal locations, were mentioned in Chapter II. But some glycogen is probably present in the normal depots in all diabetics, aside from terminal conditions. Ehrlich punctured with a trocar the livers of two human diabetics and one normal man. The liver-cells thus obtained from one diabetic contained no glycogen demonstrable with iodin, and those from the other diabetic contained far less than those from the normal man. Patients dead of diabetes may possess liver-glycogen. In

the liver of a dog dead from diabetes after complete pancreatectomy, Pflüger found a total of 0.0259 g. glycogen. Mohr has also reported glycogen in the livers of depancreatized dogs, in connection with oat-feeding experiments.

These facts are less embarrassing to the amboceptor hypothesis than to other theories of diabetes. The presence of glycogen in abnormal locations must be considered as something special under any theory; it may be a deposit of glycogen from the plasma, or a reversion from specialized to primitive cell-processes. The leukocytes not improbably possess such primitive powers, independent of the specialized amboceptor. Any glucose which may be stored by human diabetics as glycogen is presumably accounted for by such amboceptor as they may still possess. The essential problem is that of the totally depancreatized dog, which presumably has no pancreatic amboceptor. There is evidence that these dogs form glycogen, but there is no evidence that they form it from glucose. That such dogs are able to burn, and to form glycogen from, levulose is well known. It has been proved, especially by Baumgarten, that a variety of substances closely related to glucose can be utilized well in diabetes. Mohr (1) reported increase of glycogen in a diabetic dog from a meal of meat; protein is a probable source of the glycogen in diabetes. The hypothesis of a glucose-amboceptor easily explains the loss of power of the diabetic organism to assimilate glucose, and the retention of the power to burn, or from glycogen from, other substances. Other hypotheses, such as essential deficiency of the power to form or to fix glycogen, have failed to explain the whole of these facts.

6. Avian Diabetes.

The earliest workers, beginning with v. Mering and Minkowski, encountered the fact that removal of the pancreas causes glycosuria in birds of prey, but not in other avian species. But it was found that the extirpation, when complete, always results in hyperglycemia, and the presence or absence of glycosuria was therefore looked upon as a matter of permeability of the kidney. Weintraud (1) observed hyperglycemia without glycosuria in ducks. Kausch (1 and 2) removed the duodenum along with the pancreas, for the sake of perfect extirpation. Normal ducks and geese had 0.12 to 0.18 per cent blood-sugar. After complete extirpation of the pancreas, figures of 0.5 to 0.6 per cent were not rare. But only 6 out of 76 ducks and 3 out of 12 geese with

hyperglycemia showed glycosuria. Even with the highest hyperglycemia, the glycosuria was often absent; for example, one instance of 0.7 per cent blood-sugar, without glycosuria. On the other hand, percentages scarcely above the normal in the blood were sometimes accompanied by glycosuria. Feeding of dextrose (or starch) caused increased hyperglycemia and glycosuria. Feeding of levulose caused excretion of levulose; but it also formed some glycogen. The typical diabetic symptoms of increased appetite, poor digestion, loss of glycogen, and emaciation were present. Kausch came to the conclusion that the pancreas is in some way necessary for the formation of glycogen from dextrose in the liver, perhaps also in the muscles; but the pancreas is not necessary for the formation of glycogen from levulose.

It must be recognized that even when birds show glycosuria, the actual output of sugar is small. In addition to the excess of dextrose demonstrable in their blood, depancreatized birds may actually eat starch or dextrose, or receive dextrose injections, and excrete little or none in the urine. The difference from the known conditions in mammals is so great that conclusions from one cannot be applied to the other. Whatever theory be adopted to explain the lack of sugar-combustion in diabetic mammals, it is evident that diabetic birds are somehow able to burn all or most of their sugar. It may be imagined that in birds some other organ furnishes some portion of the amboceptor for glucose; or it may be that the sugar which mounts to such high values in the blood may be disposed of by some abnormal process. On this point the experiments of Giaja possess deep significance if confirmed. He found that after pancreatectomy in chickens, the blood-sugar values ranged from 0.17 to 0.29 per cent, without glycosuria. But when dextrose was injected intravenously in normal chickens, blood-sugar values of 0.24 per cent resulted in glycosuria. If it shall be regularly found that intravenously injected dextrose in these animals passes into the urine more easily than the diabetic sugar, clear evidence will thus be afforded that the latter is at least to some slight degree combined, and thus its combustion is accounted for.

Authors have shown that increase of sugar in the blood of normal animals increases combustion. Some persons have believed that diabetes consists solely in an overproduction, not a deficient utilization, of sugar. According to these persons, the hyperglycemia of diabetic birds must be due entirely to over-

production of sugar. Since generally the sugar is all burned and none excreted, it may be of interest to know whether by metabolism experiments an increased combustion corresponding to the supposed overproduction is demonstrable in these birds. The diabetic birds might be compared not only with the normal, but also with birds receiving dextrose injections. On this point, results with diabetic birds might have some application to the general theory of diabetes.

7. Reptilian Diabetes.

Nishi (2) tested the blood of normal tortoises, and found it always sugar-free. After removal of the pancreas, the onset of diabetes was slow, as usual in cold-blooded animals. But about the third day, hyperglycemia and glycosuria began, the glucose of the blood ranging from 0.04 to 0.7 per cent. Some 2 to 5 days after pancreas-extirpation, the livers were perfused, by Grube's method, with Ringer solution containing 0.3 or 0.35 per cent dextrose. A well-marked increase of glycogen was found, the percentage but not the actual weight of new-formed glycogen being comparable to that produced in normal livers.

What was said concerning the limitations of conclusions from avian diabetes applies still more forcibly to the diabetes of tortoises. The liver here may have some slight power of forming its own amboceptor, or in some other way the conditions may be different from those in mammals. But a more important consideration is as follows. The diabetes begins only on the third day. The experiments were performed 2–5 days after operation. One of the livers (No. 22) contained no glycogen; but the absence was due to original poor nutrition, because this animal was used only 2 days after operation. All the other livers contained considerable glycogen, which represented not a new formation, but a remnant of the normal stock. Nishi attributed the persistence of this glycogen to the slow chemical processes in cold-blooded animals. In other words, these tortoises all correspond to dogs in that very early period after operation, before the liver-glycogen has fallen very low. It is to be assumed that the cells cling to amboceptor fully as long as they cling to their old stock of glycogen, perhaps longer. This retained store of amboceptor, analogous to the retained store of glycogen, can account for the retained power of glycogen formation from glucose in these animals. Probability is added by the fact that the diabetic animals formed only the

same *percentage* (in proportion to the existing stock) of glycogen, and never approached the actual *quantity* formed by normal animals. The actual quantity formed by diabetic animals was very small, and perhaps stands in relation with the small stock of amboceptor as compared with the normal.

8. Ligations of Liver and Similar Experiments.

This topic opens up the three theories concerning the nature of the metabolic disturbance in diabetes:

A. Theory that normal utilization of glucose is abolished.

B. Theory that utilization of glucose is diminished.

C. Theory of simple overproduction with normal utilization of glucose.

A. Theory that Normal Utilization is Abolished.

Three sorts of evidence may be mentioned in support of this view. The first is the quantitative excretion of doses of glucose by totally depancreatized animals, as originally established by Minkowski. The second is the prevailing view concerning acidosis.

The third consists in metabolism experiments, including the D/N ratio and the gaseous exchange. The latter proves that increase of sugar in the blood normally increases the combustion. Magnus-Levy (1*A*) and others demonstrated an increase in the respiratory quotient after ingestion of sugar. Zuntz and Mering, and Wolfers, showed the marked increase after intravenous injections of dextrose. Verzár proved the increase of the quotient, and of O_2 consumption and CO_2 excretion, by intravenous injections in curarized animals. Heilner showed the increase after subcutaneous injection. Johannson found that the ingestion of sugar by normal persons causes a marked increase of CO_2 output, and that sugar can appear in the urine only during the period of the CO_2 increase. In diabetic patients, the CO_2 increase is present in some cases, in other cases diminished or absent. A long series of investigators have demonstrated the loss of the power of sugar to affect the respiratory quotient in diabetic animals and persons. Weintraud and Laves proved that the respiratory quotient of the depancreatized dog, which is not altered by glucose, rises after ingestion of levulose. Nering and Schmoller showed what large proportions of ingested sugar are excreted by human patients, together with the absence of effect upon the respiratory quotient.

Reicher and Stein found that after ingestion of sugar in normal persons, the curve of increased blood-sugar and the curve of increased combustion are parallel; the respiratory quotient rises well up toward unity. In diabetic patients under similar conditions the blood-sugar mounts higher, but the respiratory quotient rises abnormally slowly or not at all, depending on the severity of the case; a height equal to that in normal persons was not attained. Lately Verzár (5) has determined that after extirpation of the pancreas, the O_2 consumption and CO_2 excretion sink, then rise again. But the quotient sinks continuously, after several hours reaching a constant low level. During a certain brief period after pancreatectomy, intravenously injected dextrose still raises the respiratory quotient. Intravenously injected starch is not burned, in the author's opinion because not saccharified. The behavior with dextrose indicates that after pancreatectomy, some substance necessary for dextrose combustion steadily diminishes and finally disappears. Verzár's conclusion is therefore fully in accord with the amboceptor hypothesis.

The supporters of the theory of primary failure of utilization admit the possibility of a secondary overproduction of sugar, also the vague possibility that some sugar may perhaps be destroyed by some abnormal process.

B. Theory that Utilization of Glucose is Diminished.

Lepine [(1), p. 376] suggests that the depancreatized dog may burn merely less sugar than normal. Brugsch and Bamberg express a similar view. The experiments of Mohr and Heinsheimer with muscular labor, and of Lüthje (also Emden, Lüthje, and Liefmann) with cold, supposedly indicated a certain degree of power of sugar-combustion in depancreatized dogs. Seo failed to confirm the results with muscular labor, and Allard failed to confirm those with cold. The supposed burning of a little glucose under these conditions is apparently possible only in partially, not in totally depancreatized dogs.

C. Theory of Simple Overproduction with Normal Utilization of Glucose.

Claude Bernard looked upon diabetes as a simple overproduction of sugar in the liver, similar to the effects of piqûre. Chauveau and Kaufmann (1) came to the same conclusion. Pflüger

[(1), p. 440 ff] defended this theory; and Biedl (3) considers that the general trend of research is in favor of it. Finally von Noorden, leaving his former position, in the latest editions of his text-book has declared the pure overproduction theory conclusively established.

A favorite line of experiment with the upholders of this view has been the extirpation or exclusion of the liver. Kaufmann [ref. by Kausch] removed the livers of diabetic dogs, and found that the blood-sugar diminished in the same manner as in normal dogs. Supposedly, therefore, the sugar is burned equally in the two cases; and Kaufmann considered that he had proved that the utilization of sugar in diabetes is undisturbed.

Inasmuch as birds bear the loss of the liver so much better than mammals, Kausch (2) reopened the question, and studied the events in normal and depancreatized ducks and geese. He found that in both classes, after extirpation of the liver, the blood-sugar and other carbohydrate disappeared with practically equal rapidity. The higher value of the blood-sugar in the diabetic birds was compensated by injection of suitable quantities of sugar in controls.

Pavy and Siau (2) reviewed the above researches and others up to their date. On the basis of the literature, and their experiments with ablation of the liver, they came to the following conclusions. "The much-quoted statement of Bock and Hoffmann, that on shutting off the liver from the circulation the sugar quickly falls, and disappears altogether within $\frac{3}{4}$ of an hour, stands at variance with later observations. Our own results agree with those of recent observers in showing that even after the lapse of some hours, the lowest point reached by the sugar is about 0.05 %. They also show a great irregularity in the amount of fall in different experiments, and much variation in the rate of fall at different periods of an experiment. The quantity of sugar lost, looked at as a source of energy, is too insignificant to have from this point of view any physiological import."

It is now generally acknowledged that conclusions such as the earlier workers attempted from extirpations of the liver are not reliable. From this point of view the method has been abandoned. A different use for it has been found in the experiments of Porges and Salomon, which have furnished the evidence that has caused von Noorden to reverse his opinion.

Porges (4) reviews briefly the hypotheses of combustion in the body; viz., that Nasse, Chauveau, Seegen, von Noorden, and

others thought fat must be transformed into carbohydrate in order to be burned; that Rubner thought similarly of protein; but that Zunz and his pupils incline to the view that protein and fat find direct utilization like carbohydrate. Porges therefore took strong rabbits after a 24-hour fast, anæsthetized with urethane, opened them up by a crucial incision, ligated the portal vein and the aorta and inferior cava with the hepatic veins just under the diaphragm, then tracheotomized and followed the respiratory exchange for an hour. Out of 30 rabbits, only 8 lived long enough for the test. The respiratory quotient in such animals was found to approach unity (0.878 to 0.997). In control animals, it was about 0.7. In such experiments, the liver and all the abdominal viscera, and the whole of the animal below the diaphragm, are excluded. The part of the animal dealt with consists essentially of muscles. The quotients obtained indicate the burning of carbohydrate exclusively. Therefore Porges concludes that carbohydrate is the compulsory fuel of the muscles. The liver changes protein and fat into carbohydrate, and the energy of the muscles is supplied by nothing but carbohydrate. The presence and activity of the liver confuses the results of ordinary respiration experiments. By exclusion of the liver, it becomes evident that the muscles burn nothing but carbohydrate. Porges (5) defended his methods against criticisms by Verzár.

Porges and Salomon applied the above procedure to diabetes. Dogs were taken about two days after complete extirpation of the pancreas, when the D/N ratio showed total diabetes. The method was as with rabbits. Of 15 dogs, only 4 lived long enough to permit of the respiration experiments. In these four, the respiratory quotients were 1.13, 0.92, 1.19, and 0.859. In a control dog, fasting like the diabetic animals, the quotient was 0.743. The quotients found are those of carbohydrate combustion. Accordingly, the authors conclude that carbohydrate alone was burned by these animals. Therefore the totally diabetic animal is able to utilize carbohydrate; the burning of sugar in diabetes is not impaired.

Von Noorden [(1), pp. 103 and 162] emphasizes these conclusions. He considers them the first positive proof that the muscles burn solely carbohydrate, and that this power is absolutely unaltered in diabetes. The low respiratory quotients of previous workers are explained as due to the confusing action of the liver, which transforms material yielding a low respiratory quotient (fat) into carbohydrate.

The amboceptor hypothesis stands in relation with the first of the three theories, that of total abolition of the normal utilization of glucose in "total" diabetes. It is incompatible with the pure overproduction theory, and is overthrown by anything that establishes this theory. The experiments of Porges and Salomon have gained little acceptance, the criticism against them being the very abnormal conditions involved. It is possible from the present standpoint to criticize them more concretely. The authors omitted to demonstrate a disappearance of glucose corresponding to the production of CO_2 during the time of their experiments. This alone could have given their work an application (doubtful at best) to diabetes. Pavy and Siau covered this point, by proving that "even after the lapse of some hours" the loss of blood-sugar is very slight, and "the quantity of sugar lost, looked at as a source of energy, is too insignificant to have from this point of view any physiological import." Scaffidi found that ligation of the portal vein in ducks produces increase of absorption of O_2, of excretion of CO_2, and of the respiratory quotient; the quotient may rise above unity, and was interpreted by the author in favor of fat-formation from carbohydrate. Porges and Salomon could not explain their values above unity. Laves proved that after extirpation of the liver in chickens and geese, the muscle-glycogen rapidly disappears, even though the birds are fed much sugar. Thus, evidence exists that under the conditions chosen by Porges and Salomon, the blood-glucose does not disappear, the muscle-glycogen does disappear, and unknown processes enter in to confuse the respiratory quotient. The attempt to interpret their experiments as clear proof of a normal combustion of glucose by diabetic muscles obviously fails. Unless experiments prove definitely a utilization of glucose, they have no bearing upon the theory that glucose cannot be utilized, for it is well known that other substances, including some carbohydrates, are still utilized in diabetes.

The primary overproduction theory fails to explain the results of respiration experiments such as mentioned under the first theory. The primary overproduction theory is not possible except on the assumption that the body can use a certain amount of sugar, and that the excess must flow off through the kidneys — Pflüger's idea of a glass running over. In this connection the experiments of Allard (3) would seem to deserve notice; incompletely depancreatized diabetic dogs utilize a little of injected glucose; com-

pletely depancreatized diabetic dogs excrete it quantitatively. Both sorts of dogs have spontaneous glycosuria; the glass is running over; if the utilization of glucose is normal in both cases, their different behavior to injected glucose should require explanation. Finally, by means of the paradoxical law and the diuretic properties of glucose, it is possible to distinguish clearly between diabetes and those forms of glycosuria which are due to overproduction of sugar, and an end may thus be put to the pure overproduction error of diabetes. But see also (1), below.

Part II.

The second division of this chapter will deal with the following matters in connection with the hypothesis of combined sugar.

1. The mechanism in diabetes.
2. The theory of internal secretion of the pancreas.
3. Tests of diabetes.
4. Miscellaneous researches concerning physiology of sugar.
5. Behavior of non-carbohydrate substances in diabetes.
6. Differences between clinical and experimental diabetes.

1. The Mechanism in Diabetes.

Proposed and discarded doctrines concerning the essential process in diabetes are numerous. The original narrow hepatic theory of Claude Bernard was soon outgrown. The notion of De Dominicis that the disease depends upon disturbance of the external secretion of the pancreas proved unfounded. The attempt of Chauveau and Kaufmann to combine the Claude Bernard theory with the discovery of v. Mering and Minkowski gave rise to an imaginative muddle resembling the recent polyglandular doctrine, with "nerve-centers" instead of "hormones." Lepine's idea of a glycolytic ferment furnished by the pancreas has been abandoned. The idea of an intrinsic loss of power to form or fix glycogen is, as previously mentioned, on a par with the axiom that "nature abhors a vacuum"; the essential *why* remains untouched. A nervous hypothesis long existed; Pflüger was its strongest champion; but in its pure form it was abandoned even by Pflüger. The idea of a *diabetogenous substance*, an unknown poison in the body which causes diabetes unless the pancreas destroys it, is mentioned occasionally, but not seriously considered. The polyglandular doctrine substituted complexity for simplicity, confusion for clearness, many organs for one;

accepting its imaginary "antagonisms," one was just as far from understanding the actual processes of diabetes as before. The only tenable ground is Minkowski's simple doctrine of the internal secretion of the pancreas. What is needed is the knowledge how and why this secretion is necessary for normal metabolism, and why the condition called diabetes results from its absence.

The amboceptor hypothesis takes origin from the long-existing idea that the sugar of the body is normally in a state of colloid combination. It undertakes to present tangible evidence in favor of this idea. The substance with which glucose combines, or some link in the combination, is contained in the internal secretion of the pancreas. Without the pancreas the combination is impossible, and without combination utilization is impossible. An easy and satisfactory explanation is thus afforded why the assimilation of glucose may be abolished while the assimilation of various other substances may be unaffected. As stated, this hypothesis is incompatible with the pure overproduction theory of diabetes. Nevertheless, it does not necessitate the view that the overproduction of sugar is entirely secondary. Here as elsewhere, the results of investigation tend to harmonize apparently opposing doctrines, as well as to give the reasons. The pancreatic amboceptor may be compared to the mortar of a building; without it, not only is it harder to place fresh bricks and make them stay, but also the old bricks are liable to come tumbling down. The amboceptor is necessary not only for the building up but for the holding afterward. The same deficit of amboceptor which, for example, after pancreatectomy, causes the inability to burn glucose or to store it as glycogen or otherwise, may also be responsible for a primary excessive breaking down of glycogen and other reserves into glucose. The evidence for this belief consists in the easier and more intense glycosuria demonstrable in partially depancreatized as compared with normal dogs. Not only do these animals show alimentary glycosuria much more easily and intensely then normal, but in my experience all sorts of glycosuric agencies affect them more easily and intensely than normal animals. Frank and Isaac found that adrenalin produces greater glycosuria in depancreatized than in normal dogs. Thiroloix likewise demonstrated that after almost total pancreatectomy, dogs may be starved sugar-free, and then the piqûre may produce a return of glycosuria. This result, in such extremely exhausted animals, is in contrast to the faint or

negative effects of piqûre in normal fasting animals. Therefore, in reply to the old question, "Is diabetes a deficient utilization or an increased production of sugar?" it may be possible to answer, "Both." And to the similar question, "Is diabetes an impaired ability to form glycogen or to fix glycogen?" the answer may again be "Both." This increased tendency to breaking down of all the tissues is important. Without it, diabetes might be a relatively harmless glycosuria. The tissues would perhaps obtain abundant food, even carbohydrate food, from sources other than the dextrose molecule; and thus the organism might be saved from serious harm. But as it is, even the material built up from sources other than dextrose, tends to break down. There is presumably a physiological balance in the body; the existence of a certain proportion of combined dextrose is natural. When this proportion is present, its "pressure," so to speak, or the mechanism regulating sugar-production, prevents breaking down of glycogen, fat, or protein into sugar. But uncombined dextrose exerts no such "pressure"; the governing mechanism knows nothing of uncombined dextrose; in absence of combined dextrose there is a dextrose-vacuum, and all available materials are broken down at an accelerated rate in the attempt to fill the gap. This rate may be still further accelerated by influences such as piqûre or adrenalin; it may sometimes be slowed by opium or other agencies; in extreme exhaustion the process may stop. The above comparison to mass-action is in accord with observations concerning the behavior of sugar. The paradoxical law, and the parallelism of the curve of combustion with the curve of hyperglycemia, have been mentioned; and in Chapter IV it was shown that even in extreme starvation animals store glycogen richly if an excess of combined sugar is maintained in their blood by means of subcutaneous injections. It is not unreasonable to suppose that the action is reversible, and that a glucose-vacuum in the blood under otherwise normal conditions results in a breaking down of glucose-forming materials. The glucose-vacuum has reference to colloid combined glucose; it is not affected by any amount of free glucose in the blood. Poorly combined glucose may be supposed to have an intermediate action. Diabetic patients, especially when free from glycosuria, may burn more sugar when the percentage in the blood is high than when it is low, as respiration experiments in milder cases show; but the process is still slower and less perfect than the normal.

The amboceptor hypothesis combines the older beliefs in one. It is supported by some tangible evidence, and it seems to give a simple and reasonable conception of diabetes.

2. Theory of Internal Secretion of the Pancreas.

The amboceptor hypothesis is linked with that of the internal pancreatic secretion. The latter is generally accepted, but still questioned by a few writers. Hedon remarked that there can be no certainty of the existence of an internal secretion until diabetes is modified by means of some product derived from the pancreas. Pflüger carried the point to a dogmatic extreme. While the high desirability of this particular piece of evidence is to be admitted, it is not justifiable to place it wholly in a class by itself as the only real proof, for the following reasons:

A. Such evidence may be inconclusive.
B. It may be impossible to bring.
C. Other proof may suffice.

A. Such Evidence May be Inconclusive.

At the outset it must be understood that proofs in physiology are generally relative and not absolute. Those who demand an effective extract as the only absolute proof, err in demanding absolute proof, and in considering this proof as absolute. Secretin, the original "hormone," furnishes an excellent example. It is a very effective extract, and yet the whole theory of it is denied by Popielski on experimental evidence [(1) and other papers], supported by Lombroso (12). Though the attack has been meet by Zunz (2) and others, and the doctrine of Bayliss and Starling is generally accepted, the example shows that the theoretical proof furnished by an extract is relative and not absolute, like other physiological evidence.

B. It May be Impossible to Bring.

Biedl [(3), p. 20] justly holds that the inability to substitute the function of an organ by its extract can never constitute evidence against the existence of an internal secretion. The extract may be too labile, it may be present in too small quantity in the organ at any one time, its effects may be neutralized or obscured by the action of other substances simultaneously present, etc.

The weightiest evidence against an internal pancreatic secretion at present is being furnished by the brilliant and persistent investigation of Hedon with cross-transfusions. His experiments will require further notice in Chapters XVI, XVIII, and XX. The investigation has been obviously impartial, for the first results seemed to favor the view of an internal secretion; it seemed possible to delay or diminish diabetes in a depancreatized dog by continuous cross-transfusion with a normal dog. The later work indicates that the earlier results may have been due to a slight toxic action of the foreign blood. Especially in his latest work, Hedon (14) has devised a method of weighing the quantity of blood exchanged by the two animals. A dog previously depancreatized except for a subcutaneous graft was placed in vascular union with a normal dog, then the subcutaneous graft removed. Transfusion was performed for five hours; during this time diabetes appeared in the depancreatized dog, and the normal dog showed a slight glycosuria which disappeared after the animals were separated. The weights of the dogs were 6 and 5 kilos respectively; the total exchange of blood during the transfusion was estimated at 13 kilos. In another experiment, a similar transfusion failed to stop a glycosuria already begun. Hedon justly interprets the experiments in favor of an overproduction of sugar in diabetic animals.

It is obvious that Hedon's skilful procedures are greatly superior to attempts made with artificial extracts. Notwithstanding the intimate mixture of blood, one dog becomes diabetic, the other remains non-diabetic, and actively consumes the excess of sugar received from the diabetic animal, as proved by the lower blood-sugar values; slight glycosuria occurs only because the sugar is received faster than it can be fully utilized. These experiments are of the highest importance, and bring into prominence new facts; but while they do not confirm, neither do they weaken the theory of the internal secretion of the pancreas. It is to be remembered that Battelli and Stern did this identical thing with the adrenals. The adrenals were removed from a dog, and carotid cross-transfusion was established with a normal dog. With the continuous cross-transfusion in progress, the epinephrectomized dog died in the usual manner; the normal dog remained normal and died only by bleeding to death into the vessels of his companion. Any evidence by this method against the internal secretion of the pancreas holds therefore against the internal secretion

of the adrenals. Its importance in the present connection is to show that evidence for or against an internal secretion may be impossible by the method in question.

C. Other Proof May Suffice.

Though absolute proof is lacking, the relative proof suffices to make the theory of internal secretion preëminent in probability. The principal evidence may be classified as follows:

(I.) Grafts and transplants.
(II.) Parabiosis.
(III.) Diuretic properties of dextrose.

(I.) *Grafts and Transplants.* — Minkowski early transplanted the processus uncinatus of the pancreas under the skin of the abdomen, but it was objected that the pedicle of vessels and nerves remained intact and that therefore no decisive proof of an internal secretion was afforded. Later Minkowski [(1), p. 38] severed the entire pedicle of a subcutaneous graft except the artery, and found that no diabetes resulted.

Hedon (Travaux de la Physiologie, 1898) ligated the pedicle in a number of experiments, and diabetes resulted in all but three. The failures, like those of Minkowski, may be considered due to death of the graft from insufficient circulation. The three positive results stand as evidence.

Thiroloix (3) made the usual subcutaneous grafts, and in later operations removed the remainder of the pancreas and cut the pedicle of the graft. No diabetes resulted, and the graft continued to secrete several cubic centimeters of juice daily. Later, however, the graft sometimes atrophied, and then diabetes came on. Thiroloix (6) performed a further series of such experiments. After the pedicles of the grafts were cut, these dogs continued to live in fair condition with no sign of diabetes; and the grafts, though showing some atrophy, continued to secrete actively a juice possessing the usual digestive powers. When, at a third operation, the grafts were removed, the animals showed the usual typical diabetes.

Lombroso (11 and 15) has cut the pedicle of subcutaneous grafts. He found the microscopic structure of the grafts long changed, but the external secretion diminished. One of his dogs, in Minkowski's laboratory, is quoted frequently as evidence that the internal secretion and not nervous influences from the graft prevent diabetes.

The objection of Pflüger [(1), pp. 505 ff.; also (13)] to all these experiments was that some few nerve-fibres of the pedicle must have remained uncut, and that these were responsible for the prevention of diabetes. The objection is neither proved nor probable. The experiments afford weighty evidence of the existence of an internal secretion of the pancreas.

Actual transplantations of pancreatic tissue have turned out unfavorably until lately.

Thiroloix (4) noted the failures that had followed such attempts, and decided to eliminate the external secretion, the principal cause of failure. He therefore injected into the pancreatic duct (of dogs) a mixture of oil and lampblack. After three months, such a gland was completely atrophied, but the animal was not diabetic. This pancreas was then removed, cut in half, and the halves transplanted into two fresh dogs, by wrapping in the omentum. These grafts are said to have gained implantation and nutrition. Microscopically, the tissue showed ducts with cylindrical epithelium, and globular acinar cells, clear and transparent, with well-stained nuclei. Two dogs thus grafted underwent extirpation of their own pancreas. One lived 5 days, the other 9 days. Neither showed glycosuria. One had a milky cyst in the center of its graft. The brief survival of the dogs, and the incompleteness of Thiroloix's extirpations, prevent these results from being conclusive.

Auto-transplants promise better success. Martina reported having transplanted half of a dog's pancreas into the spleen. Two months later, the other half of the pancreas was extirpated. Glycosuria began on the second day after this operation, and proved permanent, the sugar varying from 3 to 9 per cent. Three months later the dog died of peritonitis originating from a fistula. Autopsy showed complete extirpation of the pancreas except the part implanted in the spleen. This part showed central necrosis, but the peripheral cells bordering the splenic tissue were intact. The author concluded only that transplantation of pancreatic tissue is possible. The method of taking so large a mass of pancreas-tissue and placing it without blood-supply in the spleen cont o unpromising, that it may be questioned whether the modified dog n of diabetes was not due to incomplete extirpation of the and creas rather than to the supposed success of the graft — espepanidy since it is not easy to remove the pancreas completely when tion e has been a previous operation.

The most successful case of this type is reported by Pratt (2). In an operation performed by Murphy, the processus uncinatus of a dog was placed in the spleen, with its vascular pedicle preserved. Ten days later the remainder of the pancreas was extirpated, a considerable abscess was found at the site of the graft, and the pedicle of the graft was cut. The dog lived for six months without diabetes. At autopsy the spleen was found separated from surrounding parts by an abscess. In it was a living pancreatic graft about 1 cm. long and 1 to 3 mm. in thickness. Microscopically the graft showed unmistakable pancreatic tissue containing a few zymogen granules. The isolation of the spleen by reason of a large abscess excludes the possibility of nerve-fibres remaining uncut. The experiment furnishes evidence in favor of the internal secretion of the pancreas, and also represents the longest known survival of engrafted pancreatic tissue. It is to be hoped that the experiment may be repeated under conditions permitting the subsequent removal of the spleen to determine if diabetes develops.

(II.) *Parabiosis.* — The principal demonstration by this method is that of Forschbach (1). Pairs of young dogs were united in parabiosis, and an interval allowed for firm union, as proved by the passage of potassium iodide from one to the other. The pancreas of one was then removed, and diabetes was found to remain absent. When the animals were later separated, the normal member of the pair remained healthy, while the depancreatized one developed diabetes.

Objections have been raised to this experiment. Pflüger interpreted the trace of glycosuria in both animals to mean that both had become diabetic. It is a fact that the depancreatized animal was close on the verge of diabetes, because a very small dose of sugar had perceptible effect upon the urine. Such a condition is explainable by the slow and difficult passage of internal secretions from one animal to another. It has been urged that the diabetic member of the pair might merely empty its sugar into the blood of its partner, which would utilize it and thus prevent glycosuria. If such were the explanation, the traces of glycosuria in the two animals could not be (as they were) practically equal; for by lactose injections it has been demonstrated that the animal receiving the injection shows far the heavier lactosuria. But the most important proof is the healing of the wound in the depancreatized animal, which is the positive demonstration of some influence from the pancreas of its partner.

Analogous evidence may be furnished by that form of physiological parabiosis or parasitism, viz., pregnancy. The injurious effects of pregnancy in human diabetes are discussed in texts and in the papers of H. Neumann. They may be supposed to be due to the slight intoxication and general nervous and metabolic strain. There are occasional examples of the opposite results. Eshner reported the case of a woman aged 27, who was excreting $2\frac{1}{2}$ litres of urine per day, containing 4.6 per cent sugar; she improved somewhat under treatment. She became pregnant, and a little over a month later the glycosuria ceased. There was albuminuria after delivery. Four months after delivery, the albuminuria ceased, and glycosuria and the other symptoms of diabetes reappeared. Planchu and Japiot reported concerning a woman who was pregnant at the age of 30 and again at the age of 33. In each instance the glycosuria disappeared at the ninth month and reappeared 2 or 3 weeks after parturition.

Such occurrences in human patients might be open to a variety of interpretations; but there is greater definiteness in the results obtained by Carlson and Drennan experimentally in dogs. They found that in very early pregnancy, diabetes follows pancreatectomy as usual. In later stages the diabetes is either diminished or absent. Their best case is that of a bitch near term; the pancreas was removed and there was no glycosuria, even when 200 cc. milk was given. The wound-healing progressed normally. The animal was becoming weak; so five days after pancreas removal, Cæsarean section was done. Glycosuria appeared within 14 hours and ran the usual course.

(III.) *Diuretic Properties of Dextrose.*—The proofs already mentioned have demonstrated with reasonable probability the humoral element in diabetes, and similarly have ruled out the pure nervous hypothesis. They have not established definitely whether the pancreas furnishes an internal secretion or whether it distoxicates some unknown poison. The distinctions found between uncombined and combined dextrose constitute a new form of evidence in favor of an internal pancreatic secretion. As against the pure nervous hypothesis, it can be shown that in none of the known forms of simple nervous glycosuria does dextrose behave as in diabetes. As against the toxic hypothesis, it can be shown that in none of the known forms of toxic glycosuria does dextrose behave as in diabetes. Also, against both these hypotheses, and against all other hypotheses, is the evidence that the distinction

lies not merely between the diabetic and the non-diabetic state, but between free and combined dextrose; for when the free crystalloid sugar is injected intravenously in normal animals, it behaves as a diuretic, as in diabetes; but under other conditions dextrose in normal animals behaves as a colloid and diminishes the output of urine.

3. Tests of Diabetes.

The two tests here referred to are the paradoxical law and the diuretic action of dextrose. They are related manifestations of the same underlying cause. Three points may be discussed in connection with them.

A. The name diabetes.
B. Experimental application.
C. Clinical application.

A. The Name Diabetes.

Since it is possible to distinguish between diabetes and other forms of glycosuria, the names should be kept separate. Though some forms of clinical diabetes may be so mild or atypical that the diagnosis is difficult, the fact remains that no metabolic disease constitutes a more distinct and characteristic entity than diabetes mellitus. Glycosuria is a variable and non-distinctive symptom. Most known forms of glycosuria are not diabetic. Diabetic patients and even totally depancreatized dogs may under certain conditions be free from glycosuria; to say that they are no longer diabetic would be absurd. There is no excuse for confusing the name of the symptom with the name of the disease. The confusion is one of thought as well as of name, as will be found in reading almost any text-book. Pflüger and a host of others have been led into error by failure to distinguish the two. There is truth in the sentence already quoted from Abderhalden: "Up to the present time the most prominent symptom, that of glycosuria, has dominated the entire investigation of problems concerning diabetes, and it is very probable that this is the reason why the disease, as a whole, is so little understood." Clear thinking on the subject must begin with a distinction between the specific disease and the non-specific symptom, and tests which permit the accurate distinction have a usefulness here.

B. Experimental Application.

In a number of later chapters it will be shown that these tests distinguish clearly between diabetes and the various well-known forms of experimental glycosuria.

A finer distinction must be recognized between simple pancreatic weakness and diabetes. As larger and larger fractions of pancreatic tissue are removed, the animal becomes more and more subject to glycosuria. The operative details and their results will be described in Chapter X. The following gradations may be recognized.

Dogs with simple pancreatic weakness. The very low dextrose tolerance is easily demonstrable, especially by the accurate subcutaneous method. Dextrose in any dose is an anti-diuretic; the dogs are not diabetic, and cannot be made diabetic by any diet. Dog 17 is an example already mentioned.

Dogs with *diabetes levis*. They are free from glycosuria on meat diet, but show glycosuria *ex amylo*. On meat diet a stock of amboceptor may be accumulated, so that a test with a reasonable dose of sugar may give a doubtful or negative result; *i.e.*, glycosuria is easily produced, but the urine may not be increased or may actually be diminished, because the accumulated amboceptor has enabled a certain degree of combination. This accumulation of amboceptor may in the mildest cases be such that a diet of bread, beyond the power of the pancreas, may cause no glycosuria for several days, till the accumulated reserve is exhausted; then glycosuria and polyuria appear as the signs of actual deficiency of amboceptor, and in this condition the tests for free dextrose are strongly positive. Dog 38 is an example already mentioned.

Dogs with *diabetes gravis*. These dogs are glycosuric on meat diet or on starvation, but the milder cases of this type can easily be starved sugar-free. After some days of this sugar-freedom with continued fasting, a slight accumulation of amboceptor is demonstrable. It is conceivable that a sufficiently small dose of dextrose might be completely assimilated and might diminish the urine. But with the doses ordinarily employed, the test is regularly positive; not all but a very large proportion of the dose is excreted; there is diuresis, but less intense than usual. The same dose in the same dog, when glycosuria is already present, is quantitatively excreted, frequently with a surplus in addition, and the polyuria is far more intense.

In other words, these animals, especially the second class, show the same improvement of assimilative power on restricted diet as human patients, and it is possible by the specific tests to demonstrate that the improvement of assimilation is due to the accumulation of a stock of amboceptor. The weakened pancreas furnishes amboceptor as rapidly as it is able. When the diet overtaxes its power, there is a continuous deficit of amboceptor and the pancreas suffers from the overstrain. When the diet is restricted so as to be easily within the power of the pancreas, the excess of amboceptor above the immediate requirement is stored by the cells of the body.

C. Clinical Application.

The test most needed clinically is one which will distinguish the slightest, earliest, most doubtful cases. The tests here described cannot be positive for this purpose. The diagnosis is required at a stage when the patient has nothing more than a pancreatic weakness; when the alimentary glycosuria which arouses suspicion does not harm him in any way, and when the condition would be entirely unimportant except for the fact that it may progress. In one sense, what is demanded is not diagnosis but prognosis. There are apparently some cases of pancreatic weakness or injury, without tendency to progress, and therefore not called diabetic. There are all degrees of severity of diabetes, even to the cases which show themselves so mildly and so late in life tnat they do the patient no particular harm. Presumably there are still milder cases, which are of the same essential nature, but never reach the point of demonstrable diabetes; as suggested in Chapter XIII, the existence of these slight tendencies helps to explain the increased incidence of diabetes in sugar-eating populations, for the excess of sugar may aggravate such tendencies. With all the existing gradations, attempts may be made to distinguish where no distinction exists. True diabetes, when not due to extensive organic pancreatic disease, is probably a disease of the nervous system which governs the pancreas. The tests of the future, involving prognosis as well as diagnosis, will probably be organic pancreatic tests, and especially nervous tests. Tests of the glucose economy have a restricted usefulness, for it is difficult to decide whether a disturbance is of pancreatic origin, and if so whether it will be progressive or not.

The two tests here discussed may be somewhat confused by renal disease and other extraneous conditions. In patients with various diseases, there are well-known tendencies to glycosuria. In patients without demonstrable or significant disease elsewhere, a lowered glucose-tolerance of itself throws suspicion upon the pancreas. Cases of low tolerance persisting for years without diabetes have been described; the trouble may nevertheless be in the pancreas, but with little or no progressive tendency. The possible clinical usefulness of the two tests mentioned must be determined by experience, but the indications afforded by animal experiments may be discussed with respect to two classes of patients, those with alimentary glycosuria and those with spontaneous glycosuria.

Alimentary Glycosuria. — In doubtful cases of alimentary glycosuria, nothing more than a pancreatic weakness can be present, but possibly of diabetic nature. Diuresis from dextrose is not to be expected; probably oliguria will be found. The dextrose paradox may be more useful; that is, if a given dose produces glycosuria, the successive increase of that dose may be hoped to produce a greater increment of glycosuria in cases of pancreatic weakness than in other forms of alimentary glycosuria. Such a test has been proposed by other writers; it has not gained very general use. But in the case of partially depancreatized dogs, previous attempts to determine a regular diminution of assimilation by feeding sugar have failed, presumably because of irregularities of absorption. With the accurate subcutaneous method, the lowering of tolerance is easily and constantly demonstrable in such animals. In spite of the comparative inconvenience of the subcutaneous method clinically, it may perhaps be advisable to make use of it in any specially doubtful case where a diagnosis is particularly desired. Such a test may perhaps be as useful in some cases of suspected pancreatitis or pancreatic tumor as in cases of suspected diabetes. The tolerance should be more accurately demonstrable by this method than by the oral method. If one dose sufficient for glycosuria is given, and some days later a much larger dose, the difference in the resulting glycosuria will perhaps be found greater in cases of pancreatic weakness than in other forms of lowered tolerance. To avoid the inconvenience of too large doses subcutaneously, it may be found practicable to give part of the sugar by mouth. If a patient with a non-pancreatic form of alimentary glycosuria receives enough dextrose by mouth to cause glycosuria, and a day or two later receives the

same dose by mouth simultaneously with a subcutaneous injection of some convenient quantity, the increase of glycosuria may not be great. In a patient with pancreatic weakness, a more decided increase of glycosuria might be expected. If there is any question of renal permeability, hyperglycemia rather than glycosuria would give the decision.

Spontaneous Glycosuria. — In cases of spontaneous glycosuria (including glycosuria *ex amylo*) the two tests mentioned should give positive results. Whether a dog's diabetes be temporary or permanent, if it is sufficiently severe to cause glycosuria on meat diet or on starch diet, during the time of this glycosuria the tests based on the diuretic and paradoxical laws of dextrose are both positive. Here again the subcutaneous test is most accurate, but the oral test is satisfactory when absorption is normal. In forms of glycosuria which may be confused with diabetes, a considerable amount of the injected dextrose may be excreted, but nothing resembling the proportion excreted during diabetic glycosuria. The diuretic test is the more striking one here; the flood of polyuria which follows a considerable dose of dextrose during diabetic glycosuria is not seen in simple nervous glycosuria. The experimental results therefore indicate that these tests will distinguish clinically between diabetes and nervous glycosuria. It is reasonably certain that cases of temporary diabetes occur occasionally; a positive outcome of these tests during the course of the glycosuria would exclude any later suggestion that the condition may not have been diabetes. The possible injury from doses of sugar under such conditions will of course be borne in mind. Rarely in infectious diseases (*e.g.*, mumps) a temporary diabetes may be present, and the same is conceivable in rare predisposed alcoholics; but the ordinary febrile glycosuria and alcoholic glycosuria, as also the "vagabond" glycosuria and other conditions, are not diabetic and will doubtless react negatively to the tests. The tests should also be of interest in "bronzed" diabetes and other doubtful conditions. In hyperthyroidism or other glandular disturbances, the tests may decide whether an existing glycosuria is toxic, or whether the pancreas is disordered along with other glands. Decision as to whether there may exist any chronic forms of glycosuria, not diabetic and not of pancreatic origin, is also an interesting possibility.

With recognition of their limitations, the tests may therefore prove of some clinical value.

4. Miscellaneous Researches Concerning Physiology of Sugar.

The hypothesis of combined sugar comes more or less closely into relation with a number of researches in a number of different directions. Among these may be mentioned the following.

Lymphagogic Action. — Sugars have been classed as lymphagogues, solely on the basis of intravenous injections. By Heidenhain and by Starling (2), for example, sugars thus injected were found to be classifiable with salts as lymphagogues of the second class. Various early researches, as by Albertoni, covered the effects of sugars upon the blood and circulation. Again, Spiro, also Pugliese, found that colloids diminish the lymph as well as the urine. It is not improbable that the effects upon the lymph will be found to vary with the effects upon the urine. If dextrose administered orally, subcutaneously, or intraperitoneally is found to diminish the lymph in normal animals, there is the very interesting possibility that it may be found to increase the lymph in diabetic animals. The effects of the other sugars upon the lymph may perhaps be found parallel to their effects upon the urine. The question seems worthy of study on this basis. The evidence may be a valuable confirmation of the amboceptor hypothesis.

Properties of Blood. — Burton-Opitz and Zanda studied the effects of dextrose upon the viscosity of the blood. Fisher and Wishart have recently brought the interesting proof that ingestion of sugar produces hydremic plethora. A specific difference between diabetes and non-diabetes, including non-diabetic forms of glycosuria, is fully to be expected.

Diffusion and Absorption. — (*a*) In the previous chapter were mentioned the conflicting results of dialysis experiments, most of them being negative; but Edie and Spence claim to find evidence in favor of colloid sugar, and Lepine and Boulud claim not only this but also a difference between normal and pathological states. (*b*) In Chapter I were mentioned the widely divergent views concerning sugar in the blood-corpuscles, the majority of investigators finding glucose present in the corpuscles, but frequently in different percentage than in the serum. Lepiné and Boulud (5) found plasma-sugar and corpuscle-sugar unequal in normal blood, but (8) equal in diabetic blood. (*c*) Magnus-Levy [(4), p. 20] mentions the phenomenon of selective absorption from the intestine, and the experiments of Röhmann, who found that of a mixture of sodium sulphate and dextrose, the latter disappeared

far more rapidly from the intestine. Friedenthal showed that the body-cells are highly impermeable to lactose. Junzo Nagano proved that various sugars, including stereo-isomeres, and the water with them, are absorbed at different rates from the small intestine. Albertoni (3) found that osmotic tension plays some part in intestinal absorption of sugars, and absorption is more rapid from hypertonic than from iso- or hypotonic solutions; but there is also a selective activity, for in solutions of equal tonicity dextrose and saccharose are absorbed more rapidly than lactose. He considers that the colloids of the blood are one factor. Comparisons between sugar in these various respects, in the normal and diabetic conditions, and in forms of experimental glycosuria, may be highly important if the results are positive. Amboceptors serve for protoplasmic assimilation; they are not necessarily demonstrable by physical tests, and do not necessarily modify absorption. The œdema which forms at the site of sugar-injection in diabetic animals is indistinguishable from that in non-diabetic animals. Authors claim that a specific difference of absorption is demonstrable for fat and protein, independent of the absence of pancreatic juice. Something similar might be demonstrable for sugars, in the form either of an impairment of absorption in diabetes (presumably specific for dextrose and due to lack of combining substance), or a more rapid penetration of the sugar due to its crystalloid character. Positive results by any of these methods would have some value as evidence; negative results cannot be conclusive.

Intestinal Excretion of Sugar. — In diabetes the kidney becomes permeable for increased quantities of sugar because of its free condition in the blood. In Chapter I was mentioned the possible interest of determining whether the intestine also becomes more permeable. The above relations of positive and negative evidence apply here. The reports of sugar in diabetic feces hold out some hope of positive results. Diabetic animals of the type described in Chapter X should constitute satisfactory material for investigations such as mentioned in this and other topics.

Jecorin. — Bing, in his careful work on blood-jecorin, failed to demonstrate an increase after intravenous injection of dextrose. He notes the abundant diuresis. The hypothesis of combined sugar does not refer to jecorin. But it is obvious that the method of intravenous injection is not the one best suited for demonstrating an increase of jecorin or other form of colloid sugar in the blood.

Blumenthal Method. — In partially depancreatized non-diabetic dogs, the subcutaneous test demonstrates the diminished power of assimilation of dextrose. It is of interest to try the Blumenthal intravenous test in such animals. It would thus be determined whether the power of the fluids and tissues to contain dextrose, and the power of the kidney to retain it, vary in a manner parallel to the power of assimilation. Judging by the behavior of levulose, it may be expected that such parallelism will not be found.

Sugar-formation. — Zuelzer (3 and 4) found in perfusion experiments with dog-livers, that the livers at height of adrenalin glycosuria or pancreatic diabetes produced more sugar than normal. He assumed that the accelerating influence in the two cases is the same, viz., adrenalin. Hinselmann (1) worked with a different method, viz., the post-mortem sugar-formation in the livers of dogs killed about an hour after pancreas-extirpation, while a considerable stock of glycogen was still present. He found sugar-formation more rapid in the livers of depancreatized than in those of normal dogs. Other experiments have had contradictory results. The above post-mortem evidence is in accord with the recognized overproduction of sugar in diabetic animals during life. But accelerated formation of sugar is not a specific phenomenon. Contrary to Zuelzer's assumption, the increased production in cells excited by nervous or humoral stimuli is different from the increased production in cells deficient in amboceptor. The difference is well illustrated by the fact that even in "total" diabetes, adrenalin and piqûre still possess the same or even an increased power of augmenting the sugar-production. The amboceptor hypothesis offers also a possible explanation for the occurrence of maltose, dextrin, or glycogen in the blood in the severest cases of diabetes. Owing to the lack of binding substance, these materials may be swept into the blood before they are properly broken down into dextrose. Other forms of glycosuria, resulting from simple stimulation of the hepatic or other cells, do not result in the casting of these unfinished materials into the blood.

Specificity. — The hypothesis of combined sugar explains satisfactorily the well-known ability of diabetics to assimilate and oxidize a variety of substances other than dextrose. Authors have brought into prominence the fact that it is essentially the dextrose molecule which the diabetic cannot attack. Baumgarten demonstrated the normal disposal by the diabetic of a long

list of substances derived from dextrose or closely related to it. Evidence to the same effect is furnished by G. Rosenfeld's lactone and Eppinger and Falk's fatty-acid compounds of dextrose [see Chapter IX]. Evidently all these substances are assimilated by means of amboceptors different from that of dextrose and not exclusively furnished by the pancreas. Some other organ may supply them [liver?], or each cell may be able to perform the entire act of assimilation independently.

5. Behavior of Non-carbohydrate Substances in Diabetes.

Mention has been made of Ehrlich's views of assimilation of foodstuffs, and the hypothesis stated by Biedl [(3), p. 14] concerning assimilative and dissimilative "hormones." Such hypotheses may include assimilative or amboceptor-like substances not merely for dextrose, but for all food stuffs whatsoever, from the simplest H_2O or NaCl to the most complex protein molecule. The assumption of "side-chains" by which the living protoplasm anchors food-molecules to itself is a very common one in metabolic literature. In the case of dextrose, there seems to be evidence that the link, or one of the links, is furnished by a specific organ, the pancreas. It is possible that the liver or other organs supply others, and that still others may be supplied by every cell for itself. Diabetes is not only important as a formidable human disease, but it and all other metabolic diseases may serve as guides to deeper knowledge of the normal processes of life. In diabetes, the economy of other substances than dextrose may sometimes be disturbed; some of the facts may bear discussion as pertaining to (A) inorganic substances, (B) nitrogenous substances, (C) fats.

A. Inorganic Substances.

Magnus-Levy [(4), p. 288], speaking of combinations by side-chains, etc., says: "A similar condition is seen in the case of chloride metabolism in starvation, where the larger part appears to be firmly bound, although — at least up to the present — we have no knowledge of a firm chemical combination in the organism."

The economy of inorganic substances may be disturbed in diabetes. Teschemacher (1) and others have reported polyuria existing before and persisting after glycosuria, and apparent transitions between diabetes mellitus and insipidus. Von Noorden denies the reality of transitions, but recognizes this occasional order of symptoms in diabetes. Falta (4) mentions the enormous

increase of weight which a diabetic patient often shows at the outset of successful diabetic treatment, due to retention of water [perhaps due to relief from the diuretic action of dextrose, but additional reasons might be possible]. Von Noorden [(3), p. 603] states that tachyuria is the rule in diabetes; bradyuria occurs sometimes. Numerous investigators after incomplete extirpations of the pancreas have reported intense polyuria without glycosuria. Further discussion will be left to Chapter XI. Nothing is certainly known concerning amboceptors for inorganic substances, but the possibility seems interesting.

B. Nitrogenous Substances.

For evidence concerning increase of nitrogen-destruction in human diabetes, reference may be made to Benedict and Joslin, Lusk, and numerous other writers. The subject is still under debate. The excessive nitrogenous excretion of the totally depancreatized dog is well recognized. Eppinger and Falta [ref. by Falta (1)] were able by levulose feeding to reduce this excretion almost but not quite to normal. There may be a question whether the increased protein destruction is partly primary, or is wholly secondary to the excessive production of sugar. Apparently a considerable primary element must be recognized, because of the numerous reports of pancreatic operations which have produced increased nitrogen excretion without glycosuria. The power to burn nitrogenous substances clearly remains. Doubt may be expressed concerning the power to build them up. Two facts, one the inability to heal wounds, the other the rapidly fatal cachexia, might be interpreted in favor of a specific impairment of protein anabolism. They apparently are not due to the failure of utilization of sugar, for two reasons. First, an equally rapid and fatal cachexia may sometimes occur in dogs after pancreatic operations, without glycosuria [Hedon's "diabetes without glycosuria"]. Second, authors have described occasional partially depancreatized dogs in which the D/N ratio was that of "total" diabetes, yet the cachexia and the inability to heal wounds or resist infection were absent. A specific impairment of absorption of protein after pancreatectomy is also claimed by a series of authors. As pointed out in later chapters, it is fairly obvious that these different disturbances have to do with different specific functions of the pancreas. The question may be whether the disturbance consists in the loss of an amboceptor (or amboceptors)

for nitrogenous substances. Magnus-Levy [(4), p. 278] in discussing the different conceptions of "living proteid" and "food-proteid," speaks of the difference as perhaps "explained chemically by regarding the surplus protein as not participating in the actual organization of the cell, and not being firmly bound, for example, in its nucleus. At least, it could be regarded as combined only temporarily by means of a side-chain." This general conception is well recognized; only it has not been customary to think of the binding substances as being supplied from a central organ. Since there is some evidence of this being the case for dextrose, and since there is also some evidence of a specific disorder of protein metabolism after total pancreatectomy and sometimes (without glycosuria) after partial pancreatectomy, there is some basis of analogy for the suggestion that the pancreas perhaps supplies substances of amboceptor nature for the nitrogenous metabolism.

C. Fats.

The subject may be discussed in three divisions: (I) Evidence for fat-amboceptors; (II) Fat-disturbances in diabetes; (III) Pathological obesity.

I. Evidence for Fat-Amboceptors.

Cohnstein and Michaelis observed that the fat of chyle, when injected into the blood-vessels or merely mixed with blood in vitro, in the presence of oxygen undergoes change in such manner that it cannot be extracted with ether. Dormeyer found that part of the fat in the blood can be demonstrated only after digestion with acid and pepsin; hence, it is an albuminous compound. Magnus-Levy [(4), p. 164] states:

"After gaining an entrance into the blood-stream with the chyle, the neutral fats remain in the circulation for the brief period which elapses before they are selected by the tissue cells for combustion or storage in the subcutaneous tissue, the paraperitoneal spaces, and the liver. Different ferments have been found to exist in the blood — some in the serum, which split the fat, and others in the red corpuscles, which convert it into the form soluble in water. It is admitted that this lipase serves for the passage of the fats from the capillaries into the tissues. The fats ought to be able to pass through the capillary wall when split up only, or in a form soluble in water, just as Pflüger considers that they pass

through the intestinal wall. B. Fischer goes so far as to refer the extraordinarily well-marked lipæmia in diabetic coma to an absence or a weakening of this ferment."

Similarly, von Noorden [(3), p. 618] says:

"The fat, as quickly as it enters the blood, and probably through some action of the erythrocytes, becomes converted into a compound soluble in water. The nature of this compound is uncertain; it may be one with lecithin. The phenomenon is termed 'lipolysis,' and the hypothetical ferment is called 'lipase.' The transformation of the fat into this compound soluble in water seems to be an essential stage before its entry into the cells. Inside the cells it becomes neutral fat again. Fischer and Schwarz suggest that in certain conditions of diabetes this lipolytic ferment is insufficient in amount, or debilitated, so that, according to the law of reversibility of ferments, its converse action preponderates. Fischer mixed normal blood with lipæmic blood in a flask, and the mixture developed lipolytic activity; the fat diminished, which was not the case when lipæmic blood alone was left in vitro."

Mansfeld and others have studied the effects of phosphorus poisoning. He found that the blood and liver of a normal dog each gives up only about half its fat to ether. But in phosphorus poisoning, the normal combined fat of the liver becomes free and can be extracted with ether. The normal state is supposed to be a fat-albumin compound. Abderhalden (p. 112) suggests a rôle of fats as solvents of other substances in the body. Eppinger and Falk have tentatively advanced the idea that carbohydrates and fatty acids are normally burned as some sort of compound, and that it is a function of the pancreas to provide for the synthesis.

Neisser and Braeuning disproved the idea that the fat-dissolving substance in the blood is a ferment. An interesting hypothetical comparison is possible between fat and sugar. Neither the free fat nor the crystalloid sugar is assimilable as such; each must become a colloid for assimilation. In the case of dextrose, a physical change is not demonstrable because of the nature of the substance; but by a physiological test, viz., diuresis, it is possible to distinguish between the free and the combined form. In the case of fat, such a test as diuresis is impossible because of the nature of the substance; but the nature of fat is such that the change in it is physically demonstrable; the droplets disappear, the fat-stains are no longer taken, it becomes water-soluble and ether-insoluble. That there is in the body a sub-

stance which forms fat into a colloid is therefore recognized. The evidence for fat and the evidence for dextrose supplement each other in very interesting manner. The question remains whether the combining-substance for fat may be wholly or partly supplied by the pancreas.

II. Fat–disturbances in Diabetes.

These may be considered as (a) abnormal absorption, (b) abnormal combustion, (c) lipemia.

(a) *Abnormal Absorption.* — The researches on this subject will be considered in Chapter XXII. A series of authors have found a specific influence of the pancreas upon the absorption of fat, independent of the pancreatic juice. The fatty diarrhea of depancreatized dogs is well known, and Lombroso has claimed that it represents an actual excretion of body-fat.

Falta (7) reported cases of hyperthyroid disease with fatty stools and lowered carbohydrate tolerance. Bittorf has lately reported a similar case, except that there was evidence of deficiency of the external secretion of the pancreas. The fact that the absorption in Falta's cases improved under radiotherapy of the thyroid does not exclude a pancreatic origin for the disturbance (perhaps through the nervous condition). They may be interpreted somewhat in favor of a pancreatic disorder distinct from diabetes.

(b) *Abnormal Combustion.* — Falta, Grote and Staehelin reported an accelerated combustion of fat as well as protein in depancreatized dogs. The power of fat-combustion in diabetes is beyond doubt; a question may exist whether a completely depancreatized animal is able to build up fatty tissue, or whether there may be a specific impairment of fat-anabolism independent of the carbohydrate disturbance. A specific impairment of the power to combine fat normally might assist in explaining the loading of the liver with "free" fat in experimental diabetes.

(c) *Lipemia.* — After the frequent reports of "milky blood" in the days of venesection, the subject of lipemia was little noticed until B. Fischer in 1903 demonstrated increase of fat and cholesterin in the blood of a diabetic patient. Some of the researches since then may be mentioned as follows.

A mild lipemia after a meal containing fat is a regular physiological occurrence in the normal organism. The milky serum thus resulting has been annoying sometimes to those who have used the serum for anti-bodies and other similar studies. Neisser and Braeuning came to the following conclusions: (1) Blood-serum of men

and animals after a 12-hour fast is clear. (2) But the clear serum contains fat, partly as a solution or colloid, and partly as a suspension so fine as to be invisible even under the ultra-microscope. (3) After a moderate fat meal, serum of normal man is always milky; after other food it remains clear. (4) The milkiness is due to fat in extremely fine emulsion (hemoconia). After butter-feeding, the fat rises in a cream when placed on ice. (5) The cloudiness of the serum varies with the kind of fat and the animal species. Rabbits show clear serum in spite of fat feeding. The hemoconia consist of the fat fed, for they are red when the ingested fat is stained with Sudan III, and the melting point varies with that of the fat fed. Butter easily gives milky serum, but oil far less so.

Further work along this line was published by Braeuning in 1909, and by Leva in the same year. Leva used especially dark-field examinations of hemoconia after fat-meals, and made comparisons between different diseases.

The lipemia of diabetics, though perhaps favored by the large proportion of fat in their restricted diet, is different from the normal digestion-lipemia. For one thing, the quantity may be out of all proportion. Lepine [(1), p. 545] states that normal human blood contains only 0.1–0.2 per cent fat. But in severe diabetes, the blood may look like chocolate, and the fat-content may be over 10 per cent. Von Noorden [(3), p. 616, and (1), p. 155–56] states 1 per cent as the upper limit of fat-content of normal blood, even in digestion lipemia. As the highest positively established values of blood-fat in diabetes he gives those of Stadelmann and B. Fischer, respectively 15 per cent and 18 per cent. Naunyn (pp. 270–71) quotes a series of analyses, of which the highest is 19.7 per cent. With even the more frequent lower percentages of 4 or 5 per cent, the serum resembles milk. Some grade of lipemia is present in a very large proportion of severe cases of diabetes. In no other disease does anything like diabetic lipemia occur. Yet in some cases, even of severest diabetes and severest acidosis, the ether-extract of the blood is not above the normal limit.

The ether-soluble substances present in excess in diabetic blood are also of different nature from those found in normal lipemia. Klemperer and Umber (1 and 2) in 1907–08 were the first to discover that increase of true fat in diabetic serum may be slight or even absent. In any event, it makes up no more than half the increase found, and the great relative increase of lecithin and cholesterin is the striking feature. Therefore instead of diabetic lipemia, the proper term is lipoidemia. This lipoidemia may be absent. It is not strictly characteristic of either severe diabetes or coma. Their second report adds that the origin of the increased fatty bodies is from increased cell-destruction. It is not from the brain nor the kidneys, neither is there a lipoid infiltration of the kidneys.

Frugoni and Marchetti published a clinical, chemical, and pathological study of one case of diabetic lipoidemia.

Reicher advanced the hypothesis that the acetone in the blood, by a sort of extraction process, withdraws the lipoids from the cells, and thus not only injures the cells, but also produces an acetone-lipoid mixture which is more poisonous than the acetone alone. Some explanation of coma was supposed to be thus afforded. The suggestion is in disagreement with the frequent occurrence of acidosis without lipoidemia.

Seo (2) found lipoidemia sometimes in depancreatized dogs. He concluded also that the ether extract of the whole blood of depancreatized dogs is markedly in-

creased as compared with normal or partially depancreatized dogs. It is rarely so excessive as to make visible milkiness. The cholesterin content varies. In general, there is no fixed distinction between the cholesterin of the blood of normal and depancreatized dogs, except in cases of visibly lipemic serum. The lecithin content corresponded to the total ether extract, therefore was increased. A diminution of corpuscle-lecithin corresponding to the increase of plasma-lecithin, as claimed by Erben, was not found. In the liver, the total ether extract was greatly increased. Cholesterin and lecithin were also increased, but not out of proportion to the general increase of ether-soluble substances.

Klemperer (2) in 1910 renewed the suggestion that the increase of lecithin and cholesterin, shown by analysis to be derived neither from the subcutaneous fat nor from the viscera, is due to the increased destruction and construction of cells in diabetes. In cell-destruction, the lipoids pass into the circulation, and in formation of new cells they are picked up from the circulation. There is no diminished utilization.

Javal, Amado and Boyet have presented a case-report with analyses. There was lipemia with increase of lecithin and cholesterin, but the organs showed no departure from the normal fat-content.

Lepine [(1), p. 485] mentions a rare case of lipuria in diabetes, in which the urine contained 0.8 per cent fat.

Diabetic lipemia is too intense to be plausibly explained by destruction and repair of cells. It is a condition peculiar to diabetes, yet not present in every case of diabetes, and its presence or absence is not determined by the severity of the case, hyperglycemia, acidosis, or other known conditions. The suggestion that it may represent a disorder of a specific function of the pancreas, distinct from the carbohydrate disturbance, seems more probable than the hypotheses now in the literature.

III. Pathological Obesity.

The sugar-tolerance of the obese is often low, and a very high percentage of all pathologically obese persons become diabetic. According to figures quoted by von Noorden [(1), p. 66], the obese constitute 15–45 per cent of all diabetics. The vague ideas concerning "lipogenic diabetes," viz., the causation of diabetes through over-loading of the pancreas with fat, are improbable and practically abandoned. Kisch (1 and 2), however, still speaks of "lipogenic diabetes." Von Noorden set up the opposite hypothesis of "diabetogenous obesity," supposing that the sugar not burned in normal manner is deposited in the form of fat in some cases and not in others. The reason for the difference is assumed to be that in some cases, the power of fat-formation is impaired along with other functions, while in other cases the fat-

forming power is retained till late. In this latter group, therefore, the sugar which accumulates in the blood is removed by the fat-forming cells, so that the patient shows the incipient diabetes by obesity, and not by glycosuria. Only when the fat-forming power fails or is over-taxed does the patient become glycosuric, although the process was actually diabetic from the outset. In the latest edition of his book von Noorden gives up most of his former arguments in support of this hypothesis, because he has now come to believe that the ability of the tissues to use dextrose is not impaired in diabetes. It is proper here to suggest, however, that his present theory of overproduction of sugar would account for obesity even better than his former ideas.

But at the present time, to attribute these effects to hyperglycemia is improbable. There is no clear evidence in favor of the view. Nothing indicates that the fat-cells retain the power to utilize dextrose longer than other cells. It is well understood that obesity frequently accompanies various internal secretory disorders, irrespective of hyperglycemia. Furthermore, this part of the doctrine is superfluous. The doctrine assumes a specific disorder of fat metabolism in some diabetic patients and not in others; this assumption suffices and is the correct part of the doctrine; the other is unnecessary. There is a question whether pathological obesity may be caused by abnormal function of various glands (thyroid, hypophysis, sexual organs) or whether it is always a disease of the pancreas, sometimes associated with other glandular troubles. At any rate, the pancreatic origin of a large number of cases of obesity may be postulated. The conception of pathological obesity, in at least a large proportion of cases, as a specific disease of the pancreas, may offer a clearer understanding of the disease itself and of its frequent relation with diabetes. It may even point the way to a specific therapy.

6. Difference between Clinical and Experimental Diabetes.

Attempts are frequently made to draw a distinction between clinical and experimental diabetes, or between a "pancreatic" form and other forms in human patients. The supposition of Lancereaux [ref. in texts] that "pancreatic" diabetes and "diabète maigre" are synonymous proved not valid. Some authors still reserve the name "pancreatic" for that minority of cases accompanied by gross changes in the pancreas. The polyglandular school undertook to set apart a "pancreatogenic" type of

diabetes, and to distinguish in various cases a "pancreatic element" from a "thyroid element," a "chromaffin element," etc. Ramond and not a few others have considered that the pancreas alone cannot explain human diabetes. Brugsch saw in acidosis a supposed fundamental difference between human and experimental diabetes. Falta (1 and 4) rejected acidosis as a point of distinction, but stated more fully than others the differences between human diabetes and that which follows total pancreatectomy in dogs. These differences may conveniently be arranged in tabular form as follows.

	Dog.	Man.
1	At height of diabetes, there is a definite D/N quotient of 2.8 to 3, as established by Minkowski.	The D/N quotient may stand far above 3 for weeks at a time.
2	There is enormous increase of the fasting protein katabolism and the salt-excretion, which may be more than three times the normal. Fat combustion is also increased.	Increase of protein katabolism is absent, both in hunger and on protein-fat diet of low caloric value.
3	At the height of diabetes, utilization of dextrose is absolutely abolished.	There is some degree of ability to burn dextrose.
4	Levulose can be utilized. It builds glycogen, spares protein, and prevents fatty liver. Levulose as well as dextrose appears in the urine.	Differences between carbohydrates vanish in severe cases. Levulose feeding may cause an equivalent increase of dextrose excretion.
5	After protein feeding, the apex of the curve of sugar excretion comes far before that of nitrogen excretion.	After protein feeding, the curves of sugar and of nitrogen excretion are parallel.
6	Fat feeding increases the sugar excretion very slightly.	Fat feeding in severe cases markedly increases the sugar excretion.

Instead of considering with Falta that this list marks out a radical distinction between clinical diabetes and pure pancreatic diabetes, most persons may rather be impressed with the broad and fundamental similarity which in general exists between the two forms. The differences may also be qualified somewhat, *e.g.*, differences 2 and 3. Contrary to the observations of Troje and other writers, Rumpff [ref. by Pflüger (1), p. 450] and von Noorden [(1), p. 93] have described human patients in whom the ingestion

of carbohydrate caused an increment of glycosuria equal and even superior to the amount of carbohydrate eaten. But irrespective whether these severest cases can utilize any sugar at all, the essential point is that differences 2 and 3 contrast the human patient only with the totally depancreatized dog. Various other authors somehow feel it necessary to attempt a strict parallelism with the totally depancreatized animal, and, this failing, to decide that human diabetes cannot be of pure pancreatic origin. But it is well known that the tiniest remnant of pancreatic tissue may alter these conditions. A partially depancreatized dog may have an intense and fatal diabetes, yet be able to utilize a little sugar, and not show the great increase of katabolism referred to.

Without entering into obscure or disputed metabolic questions, the best answer to the above table may be found in the fact that, by simple operative means, it is possible to produce in dogs a very satisfactory imitation of human diabetes, as described in Chapter X. It has been necessary to leave most of the details of the metabolism in this form of diabetes unstudied. The specific increase of nitrogen is absent at any rate; the same may be inferred concerning salts and fat-combustion; and it is to be hoped that most of the other tabulated differences will be found eliminated. These dogs are only partially depancreatized. The average human diabetic possesses a large mass of pancreatic tissue. Even the atrophied pancreas seldom or never loses all function. To attempt a strict comparison with a totally depancreatized animal is therefore a mistake. The able investigations which established the above differences retain full value; the error has been in attempting to explain them by the different specific functions of the pancreas and other organs. Rather, the explanation is found in the different specific functions of the pancreas itself. In the human diabetic, only one or a few pancreatic functions are in default; in the totally depancreatized dog they are all abolished. Any differences not thus explained must be due to species, or to accidental conditions producing or associated with the diabetes. All diabetes is pancreatic, and the carbohydrate disturbance is due to lack of the glucose-amboceptor supplied by the pancreas. It is possible that the other metabolic disturbances are due to the lack of pancreatic amboceptors for other substances, but this suggestion is not yet proved. If such substances exist for fat and protein, the pancreas is either not their sole source, or else they may be necessary for anabolism but not indispensable for combustion.

General Conclusions.

Valid objections to the amboceptor hypothesis have not been found. It stands in interesting relations with numerous facts and investigations. It gives a clear and unified conception of diabetes, and through it a deeper understanding of normal assimilation, especially the rôle of the pancreas. According to the ideas thus suggested, the emissaries of the pancreas not only meet the food-substances outside the door and prepare them for admission, but also accompany the neophyte materials through all the ceremonies of initiation, till they are at length received into full membership in the living body.

CHAPTER VIII.

LEVULOSE AND LEVULOSURIA.

Some of the properties of levulose were mentioned in Chapter II. It is reported in traces as a normal constituent of the blood, lymph, and serous fluids of the body. Chemically the similarity between dextrose and levulose is more notable than the difference; to a large extent they give the same reactions and are fermented by the same microörganisms. Matthews, Bunzel, and McGuigan have demonstrated different rates of oxidation in vitro. Lobry de Bruyn and van Ehenstein have proved that levulose and dextrose readily change one into the other under the influence of simple weak alkaline solution. Heating with dilute HCl brings about a similar change [see Neuberg]. The physiological distinction between the two is what has proved important.

There is evidence indicating that the muscles can burn levulose, but only the liver can form glycogen from it. Levulose is an active direct former of glycogen in the liver. The proof is of four sorts. (1) Experiments like those of Otto and Külz, in which animals after prolonged starvation have been fed with pure levulose and glycogen increase observed. Of the same nature is the work of Pflüger (18); in his best experiment a dog fasted 21 days, then for 6 days was fed heavily with cod-fish and pure levulose. At autopsy a large quantity of glycogen was found present, and, just as in the experiments of the earlier workers, this showed the same dextro-rotation as ordinary glycogen, and on hydrolysis yielded pure dextrose. (2) The marked increase of glycogen in frogs witnessed by Sachs after subcutaneous injections of levulose. (3) The work of Grube, who perfused tortoise-livers with various sugars, and found increase of glycogen from levulose. (4) Glycogen formation from levulose in diabetes, especially in depancreatized dogs.

Külz is quoted by texts as the first to discover that diabetic patients can utilize levulose far better than other sugars. A number of other clinicians failed to obtain such favorable results. Naunyn (p. 171) found that although levulose may be badly borne by diabetics with active glycosuria, those free from glyco-

suria may tolerate as much as 100 g. levulose without sugar-excretion. All authors are agreed that over-large doses, or even small doses repeated day after day, break down the tolerance, so that levulose is utilized no better than other carbohydrates. Von Noorden [(3), p. 547] presents a table exemplifying this fact. The paper of Petitti applies to this subject. The actual therapeutic value of levulose is therefore slight. Preparations of inulin have generally yielded little benefit, partly because of difficult digestibility; but this current opinion has recently been contradicted by Strauss (5), who recommends inulin in the highest terms, and claims that the tolerance for it is retained, instead of being lost, as with levulose. The sugar excreted after levulose ingestion by human patients is at first almost entirely dextrose; later, increasing percentages of levulose are found with the dextrose, but the latter always predominates. Minkowski applied the discovery of Külz in testing the effects of different carbohydrates in diabetic dogs. He found (pp. 70 ff) that levulose is utilized by diabetic dogs to a certain extent, but in larger doses (100 g.) it led to pronounced increase of sugar excretion. The eliminated sugar consisted partly of levulose, chiefly of dextrose. For example (p. 74), in one experiment the surplus dextrose excretion is reckoned at 45 g.; the levulose excretion was 2.6 g. Falta (1 and 4) and his co-workers have found good utilization of levulose in depancreatized dogs, and a reduction of the nitrogen-output almost to normal. More levulose in proportion to the dextrose appeared in the urine than with human patients. Probably no fundamental significance attaches to this difference, which is chiefly one of degree. In my Dog 64 on July 27, a subcutaneous injection of levulose caused a greatly increased excretion of reducing sugar, though the results were not equal to those of dextrose. The impression was gained that the levulose itself was probably an anti-diuretic, but that a large part of it was probably excreted as dextrose, which acted as a diuretic. The possibility is suggested that these dogs may approach nearer to the behavior of human patients toward levulose than totally depancreatized dogs, but the study could not be continued. The diuretic properties of levulose in normal animals indicate that a levulose amboceptor exists, but the utilization of levulose by totally depancreatized animals demonstrates that this amboceptor, unlike that for dextrose, is not derived or at least not wholly derived from the pancreas. This fact agrees with the general opinion that the liver is

the essential organ for levulose metabolism, and that an internal secretion of the liver may play a part.

The difference in the behavior of levulose and other sugars was once considered peculiar to diabetes. Zuelzer (1) found that the behavior in adrenalin glycosuria was different, because levulose appeared in the urine of an adrenalin-injected cat after a dose of only 5 g. by mouth. Zuelzer concluded from this fact that the point of attack of adrenalin is the liver. More recently, a behavior of levulose analogous to that in diabetes has been claimed for certain non-diabetic conditions. For example, Schlesinger (1) asserts that in the glycosuria which may follow tying the thoracic duct in dogs, levulose acts as in diabetes; but his results show no such extreme disparity between the utilization of dextrose and levulose as occurs in diabetes, and are probably explainable as an effect of his operation upon the liver. Neubauer (1) has found that in phosphorus poisoning, the liver lacks the power to store glycogen only from dextrose. After feeding of levulose or saccharose, considerable glycogen may be found in the liver. As in diabetes, the power to deposit glycogen from levulose is transitory; after administration for several days, glycogen is no longer stored from levulose.

The explanation of the exceptional behavior of levulose is not yet established. The most popular suggestion is that dextrose-glycogen and levulose-glycogen are somehow distinct substances, in spite of their apparent identity. The names "dextrogen" and "fructogen" have even been proposed by Koenigsfeld and approved by von Noorden. The evidence is all physiological. Pollak (1) fed dextrose and levulose to different rabbits after 4-day fasts, then injected the animals with adrenalin. He concluded that the resistance of dextrose-glycogen and levulose-glycogen to large doses of adrenalin is equal; but to small doses, levulose-glycogen is more resistant. He admits that this method can give only uncertain results. Frank and Isaac (4) interpret their phosphorus experiments to mean that the poisoned liver has not lost the power of forming but only of fixing glycogen. They consider levulose-glycogen more resistant than dextrose-glycogen, hence it remains stored when dextrose-glycogen is rapidly broken down. The clearest evidence is apparently afforded by the experiments of Porges, mentioned by v. Noorden [(1), p. 50]. After dogs were fed abundantly with rice and dextrose, both adrenals were removed, and within a few hours the liver-glycogen was reduced

to traces. But if the preliminary feeding was with levulose instead of dextrose, moderate quantities of glycogen persisted after the operation. Schwarz found in epinephrectomized rats (which lived in good condition indefinitely), that the livers were regularly glycogen-free. By feeding dextrose, he was able to cause a slight accumulation of glycogen; but levulose-feeding produced no glycogen deposit. This is somewhat notable as being the opposite to the usual distinction.

The objection to the assumption of a fructogen as distinct from a dextrogen is the lack of all direct evidence. Glycogen formed from levulose shows the same dextrorotation as dextrose-glycogen, and is broken down by acids or by diastase into pure dextrose. Lepine [(1), p. 136] describes an experiment of Rosin and Laband, in which glycogen storage was produced in a cat by means of levulose, and the glycogen of the liver then treated with diastase; the claim is that first dextrose and then levulose was obtained. The result would be of interest if it could be confirmed, but is contrary to other researches. Furthermore, if Rosin and Laband produce levulose from levulose-glycogen, they do something which the living body apparently cannot do. All evidence favors the idea that levulose glycogen is broken down in the body into dextrose, like ordinary glycogen. If levulose appears in the urine after levulose feeding, it may be looked upon as having escaped assimilation altogether. If dextrose appears in the urine after levulose feeding (as in diabetes), it means that the levulose has been transformed into glycogen or at least been taken up by the cells somehow, and then broken down or changed into dextrose. The demonstrated ability to form and to store glycogen from levulose in diabetes and other conditions is one of the proofs against the idea of an intrinsic loss of power to form or to fix glycogen.

Biedl [(3), p. 383] rejects the dextrogen-fructogen hypothesis absolutely, on the ground of the chemical identity of all glycogen. He refers to experiments of Henri, which showed an inhibiting effect of levulose upon the action of invertin; and agrees with Fraenkel that such an inhibitory effect upon the enzymes of the liver may explain the peculiar effects of levulose. Instead of a distant analogy with the action of a ferment in vitro, a closer comparison may be possible with glycerin. In Chapter III were mentioned the researches showing that glycerin prevents the glycosuria following piqûre, morphine, and amyl nitrite, and the com-

monly accepted explanation that it acts by inhibiting glycogenolysis in the liver. If glycerin were such an active glycogen-former as levulose, it is obvious that there might now be a hypothesis of a "glycerinogen" distinct from ordinary glycogen. It may be possible to determine experimentally whether any of the above-mentioned findings, on which the hypothesis of a "fructogen" is based, can be repeated with dextrose plus glycerin. In human diabetes, glycerin is generally at first well borne, but later may increase the dextrose excretion. Here its action is again comparable to that of levulose.

It is to be borne in mind that the above peculiarities of levulose under different conditions are not necessarily always due to the same cause. Even the superiority of glycogen-forming power as compared with dextrose may be reversed, as the experiments of Schwarz proved. In phosphorus poisoning or after epinephrectomy the action of levulose may possibly resemble that of glycerin. It is impossible that glycerin should permit glycogen-formation from dextrose after pancreatectomy, unless by any chance there should be a combination between them in the body, which is improbable. Evidently glycogen is formed from levulose in diabetes because the amboceptor for it is still present in the body. *The difference in the amboceptor, not a difference in the glycogen,* is the probable explanation in this case; and it may possibly be the explanation also in all the experiments previously mentioned. Since the amboceptor serves not only for building but also for binding glycogen, it is not difficult to suppose that the binding by different amboceptors may be different, and may be differently affected by different conditions. This idea has better support than the analogy with glycerin, and may offer a reasonable explanation of the behavior of levulose and also of certain other sugars.

2. Levulosuria.

Levulosuria may be treated in two divisions: (A) as a complication of human diabetes, and (B) as an independent anomaly.

A.

Levulosuria was considered rare under all conditions, until Rosin and Laband claimed to find it in a large proportion of diabetics, and in nearly all severe cases. The criteria employed were essentially the Seliwanoff reaction, and the difference between polariscopic and other analyses for sugar. Their claims were

confirmed by a number of later workers. Borchardt (1) came to conclusions opposed to the alleged levulose excretion in diabetes. For the details and literature of the subject, reference may be made especially to the papers of Koenigsfeld and of Adler.

Koenigsfeld classifies three types of diabetic levulosuria: 1. Urinogenic levulosuria, in which the patient actually excretes nothing but dextrose, but in which an alkaline reaction of the urine transforms part of the dextrose into levulose. This sort of levulosuria can be produced at will by giving the patient sufficient alkali or alkaline mineral water. Tests for true levulosuria are not reliable unless made with acid urine. 2. Alimentary levulosuria. Through some abnormality of the liver, the levulose absorbed from the food is not formed into glycogen, therefore enters the circulation and the urine. In this type, tests show that the tolerance for levulose is reduced. 3. Spontaneous levulosuria. In these cases, levulose formed in the body is excreted in the urine, so that levulosuria is present even when no levulose is taken with the food. The levulose-tests employed by Koenigsfeld were merely the Seliwanoff and polarization, therefore are not considered conclusive by the stricter critics. Von Noorden [(1), p. 113] accepts these tests as sufficient evidence.

Adler in particular casts doubt upon the adequacy of these two tests. Other substances influencing the rotation, besides levulose, occur in urine, therefore the polariscope is not dependable. Also, nitrites or other substances in urine may imitate a positive Seliwanoff reaction. Adler has tried unsuccessfully to isolate levulose from diabetic urines. No one has ever furnished this conclusive evidence. Until levulose is isolated, Adler refuses to credit its occurrence in diabetic urine.

Lepine [(1), p. 474] takes a middle position by asserting that levulose occurs rarely in diabetic urine.

B.

Levulosuria as an independent anomaly of metabolism is acknowledged by all writers to be a reality and a rarity. The earlier literature is reviewed by Neuberg, and more fully by Adler. Adler gives the following definition: *Pure chronic levulosuria is a disorder of carbohydrate metabolism, in which during a considerable period, on ordinary mixed diet, levulose is regularly excreted as the only sugar in the urine.* The total number of cases claimed in the literature is not large; and of these, according

to Adler's judgment (approved by von Noorden), only seven can stand as definitely demonstrated instances of levulosuria.

Pure levulosuria has been associated with miscellaneous conditions; with endocarditis in one case, abortion in another, transverse myelitis in another, and nervous disturbances such as neurasthenia, melancholia, and neuralgia, in others. In most cases the symptoms of mild diabetes — polyuria, thirst, pruritus, etc., — accompany the disease. The real cause is unknown. A diabetic family history is frequent. There is no known treatment except diet. Pure levulosuria sometimes disappears on withdrawal of cane-sugar and all other levulose-yielding substances from the food. In other cases, more or less strict antidiabetic diet is necessary; these are the cases in which feeding of dextrose causes excretion of levulose. The prognosis of pure levulosuria is good, for the condition tends to improve rather than grow worse, and the serious symptoms of diabetes are never present.

The most recent case-report is that of Strouse and Friedman. The patient was distinguished from all previously reported by the presence of plain signs of disorder of several ductless glands. Anti-diabetic diet at first caused the levulosuria to disappear; later a trace was present after meals, even on carbohydrate-free diet. Levulose feeding constantly increased the excretion. O. Neubauer had reported that the same percentage (15 to 17 per cent) of levulose was excreted by one of his patients, irrespective of the quantity of levulose ingested. Strouse and Friedman's experience was similar; their patient excreted 8 to 10 per cent of the dose, though the latter varied from 10 to 100 g. Tolerance for dextrose was normal; that is, 100 g. given on an empty stomach caused neither glycosuria nor levulosuria. Levulosemia is supposed to have been present, though the attempt to demonstrate it failed. Phloridzin caused glycosuria in normal manner, not levulosuria. Thyroid treatment, adrenalin injections, and pituitary tablets were without therapeutic effect.

The above reaction to phloridzin is characteristic; *i.e.*, the drug causes glycosuria. Exceptions are possible; Neubauer's patient with mixed mellituria excreted both dextrose and levulose in consequence of phloridzin. Lepine [(1), p. 277] considers that the action of phloridzin in these patients furnishes evidence that the phloridzin-effect is not a change of the renal permeability for sugar, since with dextrose and levulose both present in the blood, excretion is limited to the former.

Concerning the mechanism of levulosuria, nothing is known. Schlesinger (3) thinks it is an over-production of levulose in the liver. Koenigsfeld upholds the dextrogen-fructogen idea of glycogen, and has set up the hypothesis of a whole levulose metabolism; levulose from the food is supposed to be stored in the liver as fructogen, and this is broken down to maintain the normal trace of levulose in the blood; levulosuria is then a disturbance of the levulose metabolism, as diabetes is a disturbance of the dextrose metabolism.

Notwithstanding the considerable variations in the picture, it seems possible to form a rather clear conception of levulosuria. The associated conditions (neuroses; transverse myelitis; even endocarditis or abortion may have nervous effects) and the symptoms (pruritus, etc.) indicate that it is generally a nervous disorder, probably of the liver. It is generally recognized that the essential feature is an over-production of levulose. From the study of the tolerance in Chapter II, it is seen how easily levulose entering the blood passes into the urine; this is in contrast to the fact for dextrose. A very small excess of production of levulose above the normal traces will therefore account for the very mild levulose excretion of these patients. It seems also clear that levulosuria is frequently complicated by two conditions, viz., other disorders of the liver, and diabetic tendencies. Therefore three classes of cases result. (*a*) In the simple uncomplicated type, the tolerance for levulose and other sugars is normal. (*b*) In cases with other nervous disorders, a lowered tolerance for levulose is obviously to be expected; and as usual in hepatic troubles, the dextrose tolerance is normal. (*c*) In cases with diabetic tendencies, the levulose tolerance is normal, but there is the well-known diabetic behavior, viz., that ingestion of levulose may cause more or less excretion of dextrose. In Lion's case the three conditions were apparently present together; thus there was glycosuria increased by glucose-ingestion, and levulosuria increased by levulose-ingestion; the doses of levulose happened not to suffice for any notable increase of glycosuria. May's case of transverse myelitis is not a positively demonstrated instance of levulosuria; dextrose and levulose were present together in an alkaline urine; carbohydrate-free diet produced disappearance of both sugars. A glycosuria due to nervous disorder of the liver or pancreas is here evident, and may have been the sole condition. Otherwise, it may be assumed that the liver was better

able to hold a small than a large store of glycogen. A large amount on carbohydrate diet gave rise to excretion of both levulose and dextrose. With the smaller amount of glycogen resulting from carbohydrate-free diet, the breaking down was not in excess of the assimilative powers of the system.

The question necessarily arises as to the part played by amboceptors in the mechanism of levulosuria. Naunyn speaks of the two diseases as "levulose-diabetes" and "dextrose-diabetes"; and it is a natural temptation to jump to the conclusion that if the latter is due to deficiency of dextrose-amboceptor, the former is due to deficiency of levulose-amboceptor. But the known facts have been analyzed for the purpose of showing that the conditions in the two diseases are not parallel. Levulosuria is harmless; any troubles in relation with it come from associated disturbances, not from the abnormality of levulose metabolism. It is connected with diabetes only through the fact that the nervous disorder of the liver may be associated with disturbances in neighboring organs, one of which is the pancreas. In diabetes the dextrose tolerance is invariably diminished. In levulosuria the levulose tolerance is not necessarily diminished. Definite tests of diuresis have not been made, but the existing records indicate that levulose is not a diuretic in patients with levulosuria. Also, even when the tolerance is reduced, a paradoxical law of levulose still prevails; for Neubauer's patient excreted 15–17 per cent of the dose of levulose ingested, whether this dose was as low as 3.8 g. or as high as 50 g.; and Strouse and Friedman's patient excreted only 8–10 per cent, whether the dose was 10 g. or 100 g. Even in diabetes, though there may be intolerance for levulose, the principal excretion is in the form of dextrose; that is, it is first assimilated and changed. Therefore, there is no evidence to substantiate a claim that deficiency of levulose-amboceptor is the cause of levulosuria, either in the pure form or in association with diabetes. The mode of reasoning applies in the study of other metabolic anomalies, such as maltosuria, pentosuria, cystinuria, diaminuria, alkaptonuria, as well as to the graver systemic diseases. The assumption of a deficiency of amboceptor for some substance at some stage of metabolism may be useful if it can be supported by evidence, not otherwise. The value of the amboceptor hypothesis as applied to levulosuria may be that it introduces somewhat more definite conceptions, and distinguishes this disease from diabetes with a clearness not heretofore possible. The hypothesis itself gains

support from the study of levulosuria, by reason of this very contrast between the two diseases. The evidence in favor of the fundamental importance and distinctive character of the behavior of dextrose in diabetes is strengthened by the fact that, in a spontaneous disease superficially resembling diabetes, a sugar closely akin to dextrose may for long periods be excreted in the urine, without becoming a diuretic or ceasing to obey a paradoxical law.

CHAPTER IX.

THE OAT-CURE.

ANY discussion of the special behavior attributed to oats in diabetes must properly open with a statement of the views of von Noorden, whose discovery it is. The subject is treated in detail in his text-book. The facts were first learned from observations upon a few diabetic patients with digestive disorders. On account of the latter, they were placed on oatmeal gruel diet. Instead of increase of glycosuria, there was a decrease. Von Noorden studied the matter for nine years before he ventured to publish.

The oat-cure in typical form as prescribed by von Noorden consists in first several days of strict carbohydrate-free diet, then one or two "vegetable days," then a period of oat-days, not to be continued too long without insertion of occasional "vegetable" or strict-diet days. Generally 3 or 4 "oat days" are followed by 1 or 2 "vegetable days." A typical "oat-day" diet consists essentially of 250 g. oatmeal. To this are generally added 200–300 g. butter, and perhaps 100 g. vegetable albumin. Most patients can take cooked eggs, up to 8 per day, without harm; but in some cases eggs are injurious. Sugar-free beverages are the only other addition to the diet. Favorable cases regularly endure this diet without the slightest digestive trouble. The favorable effects in a suitable case of severe diabetes are illustrated by von Noorden in the following table, concerning a diabetic man.

Day	Sugar g.	Acetone	Perric Chloride Reaction	Ammonia g.
1. Strict diet	50.4	2.1	++	3.2
2. " "	48.3	2.4	++	3.8
3. " "	58.9	3.1	++	4.3
4. Vegetable day	28.2	2.1	++	2.9
5. " "	20.3	1.9	++	2.8
6. Oats 250g.	38.3	1.9	++	2.4
7. " "	40.3	1.3	+	1.6
8. " "	30.0	0.9	+	1.5
9. " "	20.1	0.6	+	1.1
10. Vegetable day	8.0	0.8	+	1.3
11. " "	0.3	1.2	+	1.8
12. Oat "	18.3	0.5	-	0.9
13. " "	5.6	0.1	-	0.9
14. " "	0	0.05	-	1.0
15. Vegetable "	0	0.1	-	0.8
16. " "	0	0.1	-	0.8
17. Strict diet	0	0.15	-	0.7
18. " "	0	0.18	-	1.0
19. Strict diet and 20g. bread	0	0.12	-	0.9
20. " " " " "	0	0.13	-	0.8

Thus it is seen that on the oat diet, not only do the sugar and diacetic acid disappear, and the acetone and ammonia almost vanish, but the patient who formerly excreted 50 g. sugar on strict diet has had his tolerance raised so that he now takes 20 g. bread without glycosuria.

This typical formula is varied somewhat for different patients. Not all patients react favorably. On the average, the best results are in severe cases, such as the above. Many mild cases, and a few severe ones, behave toward oats just as toward carbohydrate in other forms; that is, as would *a priori* be expected for all cases, they excrete immensely more sugar than before. The "oat-cure" is recommended by von Noorden for all patients who continue to excrete sugar on carbohydrate-free diet. He makes the following particular statements concerning it:

1. Absolutely no other carbohydrate is to be given with the oats, or the entire beneficial effect may be lost and the glycosuria enormously increased.

2. No meat whatever can be permitted on oat-days. Even eggs are sometimes harmful.

3. The oat-and-butter diet may cause diarrhea, which can be checked by opium or other treatment.

4. Especially in weak or nephritic patients, the well-known oat-œdema may appear and prove troublesome. Diuretics such as theocin often prevent or diminish this œdema and permit continuance of the diet.

For other particulars, reference may be made to von Noorden, or to the paper by Lampé and the other abundant literature. Only such facts as concern the theory are touched here. The facts themselves are under question, as noted below; but the general weight of evidence seems to favor von Noorden's contention. The explanation of this remarkable behavior in a food containing so much carbohydrate as oats has long been a puzzle, which has baffled all attempts at solution. The correct answer may be big with importance for diabetic theory or practice. Recently a more vigorous experimental attack upon this problem than ever before has begun, and it is now second to none as a subject of active investigation and discussion.

Some of the facts in connection with the subject may be grouped under four headings:

1. Glycosuric action of foods.
2. Beneficial effects of oats *vs.* other foods.
3. Peculiarities in digestion and assimilation of oats.
4. Behavior of the kidney.

1. Glycosuric Action of Foods.

The action of different foods in causing glycosuria in diabetic patients is not regularly dependent upon the quantities of starch or sugar which they contain. The different effect of equal amounts of different sugars is described in all texts, and in a number of special articles such as that of Petitti, and Falta and Gigon (1). Leaving aside levulose, lactose is generally borne best, while maltose readily causes glycosuria — more readily than its derivative, dextrose. The effects of different starchy foods belong under the next topic. The subject to be considered at this place is the widely different influence of albuminous substances of different origin in producing glycosuria.

An observation apparently forgotten is that of Eichhorst in 1871, who found that dogs fed on nothing but starch-gruel for a considerable period, and then suddenly given a large quantity of meat, in a minority of instances show glycosuria on the first or second day of meat-feeding, but not thereafter. Five of Eichhorst's dogs behaved thus, and the glycosuria resulting from meat diet ran even above 2 per cent. Straub (1), confirmed by Rosenstein, found that preliminary meat-feeding favors the occurrence of CO-glycosuria. When animals have been fed with pure carbohydrate, or abundant carbohydrate with inadequate albumin, carbon monoxide fails to cause glycosuria. Seelig found that ether anæsthesia produces more or less glycosuria in dogs that have been fed with meat, whereas preliminary feeding with carbohydrate prevents the glycosuria.

Mention has been made that no meat may be given during the oat-cure, or all the benefit is likely to be lost. Such effects in diabetes have been observed apart from the "cure." Lepine [(1), pp. 512–14] describes some of the observations of various authors, beginning with Külz, of the different effects of meat, casein, and yolk and white of egg. The most complete clinical study of this question has been made by Falta and his co-workers

[see Falta (2 and 3), and Falta and Gigon (1)]. Some patients show the differences more plainly than the majority. Falta and Gigon found that in such cases, protein distinctly lowers the assimilation of carbohydrate, the additional excreted sugar being more than could come from the added protein, and therefore being derived either from carbohydrate of the food, or from other food-protein, or from body-protein. The differences between different proteins are described, meat being found specially harmful as compared with vegetable albumin. Falta describes other cases, in which a sudden increase of protein actually causes greater glycosuria than an equivalent addition of carbohydrate to the diet. As Falta puts it, some patients are more "sensitive" to protein than to carbohydrate.

Analogous experimental observations have been made. Sandmeyer, in studying the form of diabetes named after him, discovered that fresh pancreas, when fed to his dogs, instead of diminishing the glycosuria really acted as a glycosuric agent. Sugar-excretion was increased 3 to 14 fold. The action was attributed to improved digestion, especially in connection with the glycogen of the horse-meat which was fed simultaneously with the pancreas. Minkowski (2*A*) adopted this explanation. Pflüger (13) confirmed Sandmeyer's observations. Lüthje (1*A*) also found increase of sugar from pancreas-feeding, and attributed it to the split-products of protein. Rosenberger (p. 106) states that large doses of pancreatin fed to normal rabbits cause glycosuria. Reach (2, 3, especially 4) showed that, to cause glycosuria in partially depancreatized dogs, neither pancreas nor horse-meat is necessary, but that any kind of raw meat acts the same. The same animals can take cooked meat in any quantity without glycosuria. The hyperglycemia and glycosuria produced by raw meat were proved by suitable analyses to be not due to better digestion or absorption. Reach infers that the raw meat has a "toxic" action, which "paralyzes the functions of the pancreas."

2. Beneficial Effects of Oats vs. Other Foods.

Von Noorden has claimed throughout that the value of oats is preëminent. In this contention he has been supported by the majority of other observers. Other carbohydrate "cures" have been devised by different persons, — barley, wheat, potato, milk, etc., — but have failed to become established on the same level

with oats. On the other hand, it is now generally conceded that the difference between oats and other grains is quantitative, not qualitative.

The study of Lampé has already been mentioned. Westenrijk, working in von Noorden's clinic, describes a decided difference between oat days and wheat days in favor of the former. Falta (5) says that the potato-cure is without value, and the milk-cure is nothing but under-nutrition, but that the oat-cure is very useful in many cases. He rejects Naunyn's fermentation hypothesis, and considers it possible that something in oats may stimulate the internal secretion of the pancreas.

Jastrowitz and Beutenmüller found that on oat-days the sugar excreted was always less than that ingested. The effect was not dependent upon the severity of the case. Repetition of the oat-cure in the same patient was not always followed by the same results. Though acidosis diminished promptly, neither the oats nor large doses of soda could make it disappear entirely. The authors think that retention of both sugar and acetone-bodies in the blood has some share in the results.

Blum has asserted that there is no preëminent value in oats. Generally only light cases do well on grain cures, and the kind of grain used is immaterial. He has seen suitable patients improve or become actually sugar-free on a diet of wheat-flour and fat. He uses a "wheat-cure" for many cases, but no "oat-cure."

Von Noorden acknowledges Blum's contention that the carbohydrate-tolerance is raised by the preliminary strict-diet and "vegetable" days, but denies that the whole benefit of the "cure" lies herein, or that wheat is on a par with oats. The patients treated by Blum's régime were only the milder sort of diabetics. In such, von Noorden acknowledges that a few days of restricted diet frequently raises the tolerance so that any form of carbohydrate — oats, wheat, barley, rice, bread, potatoes, milk, even sugar — may be borne in large quantity, *provided no meat is given with them*. In such cases there is practically no difference between oats and other carbohydrate. But in the more severe types of the disease, there is no difficulty in recognizing the superiority of oats. This view is confirmed by Falta (8), by Lampé, by Baumgarten and Grund, and others.

Klemperer (3) supports Blum's claims and carries them to their logical conclusion. He presents clinical records to show that in the severest cases of diabetes, pure dextrose behaves very much

like oats or wheat, if given in the same way, without meat, and preceded and followed by vegetable days. That is, patients with acidosis, who continue to excrete sugar on carbohydrate-free diet, are given a day or two of vegetables, followed by a series of sugar-days, on which they eat sanatogen, butter, perhaps eggs, bread and other foods, — but no meat whatever, — *and* 100–150 *g. pure dextrose each day* in small divided doses. In favorable cases, just as with oats, they assimilate most of the dextrose and excrete only a small and decreasing amount; the acidosis disappears; and they become sugar-free on the succeeding vegetable days. Meat spoils the results; even eggs may do so. Vegetable albumin is well borne.

The advocates of the oat-cure do not consider its position absolutely unique. Some authors have arranged the different grains in a series according to their relative effects in diabetes. Barley is to be placed next to oats, according to Lampé's observations, with which Klotz agrees, and which Magnus-Levy accepts. Of foods other than cereals, von Noorden is now emphasizing the value of bananas in the dietary of diabetics, placing them above everything but oats. Though not as generally useful as oats, in some patients bananas yield the same sort of results. Von Noorden hopes that still other carbohydrate-containing foods may be discovered which possess similar properties.

Abt and Strouse have reported good results from oatmeal in two cases of diabetes in children.

Magnus-Levy (2 and 5) supports oatmeal as the most valuable of the grain "cures." He concedes that no fundamental or qualitative difference exists between oats and other grains; but practically and quantitatively, the results from oats are better. The problem of carbohydrate "cures" is, that a moderate quantity of oats or other grain added to anti-diabetic diet causes great glycosuria, while five times that quantity of oats given alone causes little glycosuria. The work of Naunyn is quoted, proving that the glycosuria in diabetes is reduced by reducing the quantity of meat eaten ("paradoxical tolerance"). Also, the benefits of hunger-days or vegetable days are dependent upon exclusion of meat. Meat will increase glycosuria when even a larger quantity of vegetable albumin fails to do so. There must accordingly be a harmful property in certain foods; and the general benefit attaching to all grain "cures" is the exclusion of these harmful foods, such as meat. To account for the special advantages of oats, the

presence of "help-substances" has been supposed. Oat-extracts may be considered a failure, in view of their abandonment by His. Magnus-Levy reports likewise his own negative results with them. Also, when most of the starch was removed from oats, the good results in diminishing glycosuria, etc., were not greater but rather less than with natural oats. The purified oat-starch itself is tolerated better than other kinds of starch, and benefits the patient in manner equal to the full oats. The author concludes that the special virtues of oats as compared with other grains are attributable to a special structure or other peculiarity of the starch grains.

Baumgarten and Grund assert that oat-starch is not comparable to the full oats in value for diabetic therapy, nor can any part of the grain take the place of the whole. Grund affirmed this statement at the 1911 Congress [für innere Medizin].

Schmidt suggested that the different sizes of starch grains, the different temperatures at which they swell in water, and their different digestibility as shown by tests with different raw starches in healthy subjects, may play a part.

All authorities are agreed that oats, to be of any value in diabetes, must be given in some boiled form, that is, as oatmeal mush or gruel. Baking seems to destroy the virtues, for oat-bread is just as harmful as any other carbohydrate. Von Noorden even draws distinctions between different brands of oats. Luckily, American oats are beneficial.

The opinion of several speakers at the 1911 Congress, that oat-cures depend for their good results essentially upon the mere reduction of protein intake, was combatted by Falta and others, who support von Noorden's assertion that similar benefits are obtained from oats when, by addition of vegetable albumin, the total nitrogen of the food is brought up to equal that of normal diet.

Strauss (5) is one of the numerous recent writers who have become convinced that the effect of oats is not as specific as formerly supposed. It is largely a question of individuality of patients. In a few cases, a milk-cure is very beneficial. He has compared the effects of wheat and oats, and found no uniform superiority of the latter; for some patients oatmeal is superior, for other patients it is definitely inferior to wheat. The vegetable diet is one important element; a strict and constant formula for the "cure" is not necessary. But in particular, contrary to

other authors, Strauss has found inulin well digested and assimilated; the acidosis and general condition are benefited, and there is no subsequent loss of tolerance, as with levulose. Inulin has proved superior to both wheat and oats, and is strongly recommended as a "cure." Inulin-rich vegetables may be useful when the pure inulin is too expensive.

In review of the clinical evidence concerning the special merits of oats, the remark of His at the 1911 Congress may be repeated; that the observers are all highly reliable men, and each of them tells a different story from the others. A conservative judgment may be as follows: that much of the benefit is due to the complete withdrawal of meat and other features of the "cure"; that benefit is obtainable from other cereals or carbohydrate foods by following the same program as with oats; but that the greater weight of opinion is still in favor of a quantitative superiority of oats, in that it produces greater benefits in a greater number of patients.

3. Peculiarities in Digestion and Assimilation of Oats.

Naunyn advanced the hypothesis that oat-cures act by starting up extensive fermentative processes in the intestine, with the result that the carbohydrate is absorbed not as dextrose but as fermentation-products, and these can be readily burned by the diabetic. In 1905 Lipetz, a pupil of Naunyn, undertook to show, by a method of counting the bacteria of the feces, that the number is increased during oat-cures, supposedly in consequence of the fermentative processes. The importance of the fermentative factor is accepted by Magnus-Levy (5), Lüthje (4), and a number of other writers. Von Noorden has steadily opposed this view, emphasizing the absence of flatulence, the generally good digestion and stools, and the striking nutritive value of the oat-cure. The fermentation hypothesis has given rise to a vigorous school, who are supporting it with most active research.

The work and opinions of Rosenfeld must first be mentioned in this connection.

Rosenfeld (1 and 2) has long devoted himself to researches concerning acidosis and the pathological distribution of fat. He (3 and 4) has laid down a principle often referred to, placing the fat and the glycogen of the liver in opposition. Various agencies — phosphorus, phloridzin, arsenic, antimony, chloroform, alcohol, overheating, pancreas-extirpation, etc. — lead to fatty liver, and in every instance such a liver is glycogen-free. On the other hand, feeding of sugar causes glycogen-formation and prevents fatty liver. In phosphorus poisoning sugar does not form glycogen, and therefore does not prevent the fatty change. Rosenfeld (5) makes an equally

oft-quoted statement, when he represents fats as difficultly combustible substances, like coal, and carbohydrates as readily combustible substances, like kindling. The carbohydrate is necessary to kindle the fat. A glycogen-containing liver can therefore burn fat, and does not become pathologically loaded. A glycogen-free liver cannot thus burn its fat, and accordingly fatty liver results. Up to this point, therefore, two principles have been laid down; that fat burns only in a fire of carbohydrate; and that glycogen in the liver prevents fatty liver.

The occurrence or prevention of fatty liver in fasting phloridzinized dogs is consequently adopted by Rosenfeld as a standard test in a long series of experiments. Dextrose can prevent this fatty change, but mannit, glucosamin, and glyconic or saccharic acid are unable to do so. Therefore if a carbohydrate-fat compound exists, it must be formed with the dextrose molecule and not with its derivatives. After the phloridzin fatty liver is produced, it can be cured by feeding dextrose. But the fatty liver of a dead animal was not changed by perfusion with blood containing dextrose, and moreover, dextrose injected intravenously in large quantity in living animals generally did not alter the fatty liver. Neither did the muscles form glycogen. Dextrose by rectum was equally ineffective. That is, dextrose given by mouth forms glycogen and prevents fatty liver; dextrose given by any other route does not form glycogen nor prevent fatty liver. A third difference is also affirmed by the author, namely that dextrose given by mouth in phloridzinized animals is excreted, whereas when given intravenously it is largely utilized. The same is said to be true of depancreatized animals; incomparably better utilization intravenously than by mouth. These three differences are alleged to distinguish between two modes of utilizing dextrose in the body; one the *glycogenic*, when dextrose is given by mouth; the other the *aglycogenic*, when dextrose is given by any other route. The diabetic is still able to form glycogen, but unable to utilize carbohydrate in this form. Dextrose which takes the *aglycogenic* route can still be utilized. The role of the liver is determining; *glycogenic* is synonymous with *hepatic* route; *aglycogenic* is synonymous with *anhepatic*. Phloridzin glycosuria is also said to remain absent in frogs after removal of the liver and in dogs after Eck fistula. Reference is made to the report of Reschop in Külz's book, to the effect that a severely diabetic patient was able to assimilate sugar by gargling it (*i.e.*, sugar absorbed from the mouth and pharynx can be utilized); also to Arnheim's observations concerning the assimilation of sugar-enemas in diabetes.

Rosenfeld (6) tried feeding glycerin to phloridzinized animals. He concludes that glycerin sometimes takes the "glycogenic," sometimes the "aglycogenic" route, and that its different behavior in different cases of human diabetes is thus explained. Carbohydrate utilized by the "aglycogenic" route is claimed to have anti-acetonuric effects, just as by the "glycogenic" route. Therefore, in the treatment of diabetic coma, the author strongly recommends the intravenous infusion of large quantities of dextrose.

Rosenfeld (7) presents a few records showing the effect of intravenously injected dextrose in diminishing the acetonuria of fasting phloridzinized dogs; it also caused a remarkable fall in the excretion of nitrogen. A similar diminution of nitrogen is claimed in dogs simply fasting, without phloridzin. The effect is alleged to be due not to a sparing action, but to avoidance of the liver by the intravenous route. The liver is set forth as the central organ of metabolism; it influences carbohydrates so as to make them inoxidizable by the diabetic; it influences them so as to make them kindling-materials for fats; and it governs the nitrogenous metabolism.

Rosenfeld (8) places different protein substances in series on the basis of their power to form glycogen and prevent fatty liver. Meat is the most effective in this respect, edestin the least effective.

Rosenfeld (10) publishes glycogen-analyses of dog-livers, showing that after feeding 8 g. dextrose per kilo, the maximum glycogen-formation amounted to 22 per cent of the dose administered, and much glycogen was still present 16 hours later. After injection into the jugular vein of 11 g. dextrose per kilo (injection-time about 1 hour) the maximum glycogen-formation in the liver amounted to 15 per cent of the dose administered, and within 10 hours this had nearly all disappeared.

Klotz has been one of the most diligent investigators of this subject.

Using the Rosenfeld test, viz., the comparative percentages of fat found in the livers of fasting phloridzinized dogs, Klotz (1) obtained the following values:

	Fat in Liver.
After feeding wheat flour	12 per cent
After feeding rice flour	20 per cent
After feeding potato flour	20.5 per cent
After feeding rye flour	26 per cent
After feeding barley flour	35 per cent
After feeding oat flour	43 per cent

His conclusion is that oatmeal is absorbed largely in the form of fatty acids, hence does not prevent fatty liver. Barley is next to oats, in harmony with its behavior in diabetes. The others are absorbed mostly as dextrose, and therefore are able to prevent fatty liver, wheat standing as the antithesis of oats. Various arguments are presented concerning the possibility that different cereals may behave differently during digestion.

Klotz (2) makes similar statements. Klotz (3) explains his views somewhat more fully, supposing that oats, and to less degree barley, are absorbed not as dextrose, but as acid products of fermentation; as such, they constitute "anhepatic" carbohydrate, take the "aglycogenic" path, and thus are burned by the diabetic and influence his ketonuria favorably. He attributes very great importance to the intestinal flora in this process. In some patients, the intestinal flora or other unknown conditions are unfavorable. Here the oat-starch is absorbed as dextrose, takes the "hepatic, glycogenic" route, and aggravates the diabetes. Klotz supports the fermentation hypothesis of Naunyn, opposes von Noorden's idea that fermentation necessarily means meteorism, and approves Lampé's arrangement of the cereals in a graded series according to their diabetic usefulness. He believes with Rosenfeld that glycerin sometimes takes the "glycogenic," sometimes the "aglycogenic" route.

Klotz (4) undertakes to support his views by experiments in vitro. He admits that weighing of bacteria in the feces gives only uncertain results, and his own experiments show that any differences due to oats are very slight. Investigating the effects of pancreatic juice upon the different starches, he found that both oats and wheat yield sugar, though in slightly different actual quantity and proportions of dextrose and maltose — "in narrow limits," he admits. Similarly, in testing the action of acid-forming bacteria, he found that oats generally but not always yield more

acid than wheat. But, in general, he claims that these experiments support his former opinion that wheat-starch is absorbed as dextrose, but oat-starch as oxidation-products of dextrose.

Klotz (5) believes he has found the explanation of the occasional atypical results met with in his former animal experiments. He fed dogs abundantly for a period with carbohydrate and milk, in order to produce a flourishing acidophile flora and a strong lactase; then they were starved for 5 days, then given phloridzin and wheat or oat feeding. Since the fermentation was active, typical fatty liver was found not only with oats but even in some cases with wheat; that is, the starch was absorbed mostly as fatty acids. Other dogs received preliminary meat-feeding, then the starvation, etc., as above. Here glycogen-livers instead of fat-livers were encountered not only with wheat, but even with oats, because of poor fermentation on the part of the proteolytic flora, and consequent absorption of the starch as dextrose. He assumes that the unfavorable results of oats in occasional diabetic patients may be attributed to peculiarities of the intestinal flora. He also claims, following up Stoklasa's idea, that potassium phosphate fed as a catalyzer has special influence upon the outcome of experiments by his method.

Klotz (6) discusses the general importance of the intestinal flora in health and disease. Klotz (7) sums up his work and opinions, and reviews considerable literature bearing upon the fermentation hypothesis. Two features are brought into special prominence; one, that oat-starch ferments more easily than wheat-starch; the other, the importance of the intestinal flora. With a sufficiently flourishing acidophile flora, wheat or other cereals are absorbed in the form of fermentation products, almost like oats; and thus are explained the numerous favorable reports concerning various carbohydrate "cures" besides oats.

Klemperer (3), in connection with his experiments of feeding pure dextrose in diabetes, assumes an influence of the intestinal flora. Meat is injurious because it favors a proteolytic flora. Purely vegetable feeding gives rise to a fermentative flora; any kind of starch, or dextrose itself, will serve precisely the same purpose. The acid products of fermentation are supposed to be not only themselves utilizable, but also to have an effect in stimulating the combustion of sugar in the cells of the body.

Magnus-Levy (2 and 5) approves the work of Lipetz and of Klotz, and believes there is some value in Rosenfeld's idea of opposition between fat and glycogen in the liver. Fermentation is probably not the only explanation of the effects of oats, but probably plays a part. The fermentation products may not only be utilized, but also may assist in the assimilation of other carbohydrate. It is wrong to suppose that the whole or most of the starch is absorbed as fermentative products. The work of Klotz has not only given some experimental basis for the fermentative explanation of the action of oats, but by inference may be applied to the problem of cellulose digestion. That is, in the question

whether cellulose is absorbed as dextrose or as acid products, the latter supposition now appears the more probable.

Lang studied the behavior of a series of starches under the influence of pancreatic diastase. He found that they vary somewhat in the rapidity with which they break down into dextrin, and vary in a still different order in the rapidity with which these intermediate products break down into sugar. But there is no distinction between oats or any of the rest sufficient to explain the differences observed in diabetes.

Baumgarten and Grund [see also Grund] failed to confirm the results of Klotz with the Rosenfeld method. No such marked fattiness of the liver as described by Klotz after oat feeding was ever seen in their experiments.

Mohr (3) opposes strongly the whole idea of Rosenfeld and of Klotz. He considers that two processes are concerned in the production of fat-liver, viz., fatty infiltration and fatty degeneration. The Rosenfeld extraction method yields no information concerning such finer distinctions. He refers to experiments by his assistant Jastrowitz, who obtained by oat-feeding in depancreatized dogs an accumulation of liver-glycogen beyond the limits of experimental error. Mohr concludes that the unique properties of oats are not due to fermentative decomposition, nor absorption in form other than dextrose. Oat starch is absorbed in just the same form as other carbohydrate.

Boruttau stated at the Congress of 1911 that in his experiments to date, no difference has been observed in the utilization of oats and other forms of starch by depancreatized dogs.

Lüthje (4) believes that fermentative processes play a part of some importance in the oat-cure.

Falta (8) asserts that no reason is known for the superiority of oats. He disbelieves the fermentation hypothesis altogether, on the basis of the disappearance of acetone and the restoration of nitrogenous equilibrium in favorable cases, and the large sugar-excretion in unfavorable cases. All these facts point to absorption in the form of dextrose.

The idea that carbohydrate may be utilized by diabetics if absorbed in some other form than dextrose is in accord with known facts. Mention has previously been made of the experiments of Baumgarten (1 and 2), proving the ability of diabetics to burn a list of substances closely related to dextrose. Similar evidence is furnished by the synthetic substances prepared by Rosenfeld and

by Eppinger and Falk. On this basis, it would not be impossible to set up a speculative hypothesis that, instead of a split form, oat-carbohydrate may be absorbed in some combined form.

G. Rosenfeld (9) has prepared the lactone of α-glycoheptonic acid, a seven-carbon-sugar product. It is described as being pleasantly sweet to the taste, useful in sweetening diabetic food, and readily assimilated and oxidized by diabetic patients. It diminishes rather than increases glycosuria, but has very little influence upon the ketonuria. F. Rosenfeld has published a favorable notice of the above preparation. Pringsheim has also reported favorably, saying that combustion of the lactone is complete in doses up to 30 g., and in some cases acetonuria is diminished. Strauss (5) also recommends it.

Eppinger and Falk were led by the simultaneous excretion of acetone and sugar to take up the idea that fat and carbohydrate are normally burned in a form of combination, and that the pancreas normally performs the synthesis of the two. The suggestion in some respects resembles Rosenfeld's "fire of carbohydrate" notion. They call attention to the easy chemical production of fatty-acid compounds of dextrose. Pentacetylglucose crystallizes and can thus be purified. Mono-, di-, and tri-acetylglucose are harder to purify. They injected such compounds subcutaneously in dogs. After injection into a normal animal of 50 g. of a mixture of mono- and diacetylglucose, only 7–8 g. appears unchanged in the urine. [Size of dog not stated.] Depancreatized dogs show the same behavior. Other compounds related to the above act somewhat less favorably. The authors are continuing their work, and suggest the possibility of valuable foods for diabetics.

If such substances, in addition to their theoretical interest, are to have practical value, it is obvious that they must be prepared in some form capable of oral assimilation, since subcutaneously injected carbohydrate does not diminish acidosis.

Before leaving this topic, a few criticisms seem in order. It would seem that Rosenfeld's theories, based on his earlier interesting work, are now leading him into inaccuracies both of reason and of fact. The following may be pointed out. (*a*) The experiments, in which he claims to prove that phloridzin glycosuria is prevented by removal of the liver in frogs and by the Eck fistula in dogs, are contrary to the well-established facts concerning phloridzin [see Chapter XV]. (*b*) In his claim that "aglycogenic, anhepatic" dextrose can be utilized in diabetes, he makes use of the gargling experiment of Reschop, in Külz's book, published in 1874. This patient was free from glycosuria, and remained so, though he must have swallowed much of the sugar; Klemperer's experiments give the reason for the absence of glycosuria. Rosenfeld also refers to the assimilation of sugar-enemas by diabetics as reported by Arnheim; here the slow absorption is a satisfactory explanation. On the basis of these and his own experiments, he maintains the hypothesis that sugar does

not form glycogen when introduced with avoidance of the liver, *e.g.*, when injected intravenously, or absorbed from the mouth or rectum. Here he ignores completely the fact that investigators of the highest rank have observed rich glycogen-formation from subcutaneous injections of dextrose or levulose. Also my experiments in Chapter IV show that this occurs even in advanced starvation. De Filippi's Eck-fistula experiments showed a very heavy formation of glycogen in the muscles. (*c*) The claim that dextrose does not form glycogen when introduced intravenously is contrary to fact. Rosenfeld's failure to obtain glycogen-formation in perfusion of mammalian livers is not surprising. Grube and others have proved that glycogen formation is obtainable by perfusion, especially in livers of cold-blooded animals. Recently Freund and Popper have demonstrated glycogen-formation in the liver from injection of dextrose into a systemic or mesenteric vein. The latest work of Rosenfeld (10) is in substance a withdrawal from his former position, for he demonstrated glycogen formation in the liver after dextrose injections into the jugular vein. The percentage (15 per cent maximum) compares very favorably with that from dextrose feeding (22 per cent maximum) when allowance is made for consumption of sugar by the muscles, and for the injury caused by large intravenous injections. The latter explains also the more rapid disappearance of the glycogen. (*d*) The diminution of nitrogen excretion after intravenous injection of dextrose in phloridzinized animals, as reported by Rosenfeld (7), is so extreme as to indicate probably experimental error or injury to the animals from the large doses. The dogs were not always catheterized. Normal fasting animals are said to show the same drop in nitrogen as phloridzinized animals. In my experiments, it has not been possible thus to reduce the nitrogen output by intravenous injections of dextrose, nor was anything of the sort found in the careful experiments of Hedon, Arrous, Lamy and Mayer, Fleig, and other authors mentioned in Chapter VI. (*e*) The assertion that not only phloridzinized animals but also depancreatized animals utilize dextrose when it is injected intravenously is incredible. Observations by Falta, Grote and Staehelin, and others, prove that considerable dextrose can be retained in the diabetic dog's body, without being assimilated at all. Obviously, the chance is greatest after the renal and systemic injury produced by large intravenous injections. Rosenfeld gives no blood-sugar analyses, no respiration experiments, and no proof

of a total pancreatectomy. (*f*) The claim that parenterally injected dextrose successfully combats acidosis is contrary to the findings of others, especially Waldvogel, that parenterally injected dextrose increases rather than diminishes acidosis. (*g*) The general claim that it is the liver which makes carbohydrate inutilizable by the diabetic is wholly untenable. If it were correct, the Eck fistula would be a cure for diabetes. (*h*) Rosenfeld's finding of the frequent opposition between fat and glycogen in the liver is one of the interesting parts of his work. But it is generally recognized that the rule is not uniform nor absolute. Also with subcutaneous injections of dextrose during starvation, there is sometimes found a considerable amount of fat along with glycogen in the liver; for example in Cat 59, the liver contained 4.4 per cent glycogen, yet gross and microscopically was full of fat. Rosenfeld's own tables show the discrepancies which have caused others to report negative results from his method. Occasional values in the controls run above those in the test-animals. A comparison may also be made between different publications. Rosenfeld (5) refers to the glycogen percentages after giving dextrose by rectum (8.3, 1.8, 2.3, 1.) or intravenously (1.5, 2.6 per cent) as "unbedeutend," and finds them incapable of preventing fatty liver. But Rosenfeld (6), in glycerin-feeding experiments, found 1.33 as the highest glycogen-percentage, and this had a very marked effect in preventing fatty liver.

The counting of fecal bacteria, as by Lipetz, is recognized as an inconclusive procedure. The experiments of Klotz are much more valuable, especially as negative evidence. They do not serve to establish the fermentation hypothesis, for the following reasons.

One objection may be that a complex question has not been separated into its simple parts, either by Klotz or by others. (*a*) What is the subject-matter of Klotz' research? It is the question whether oat-starch is absorbed in the same form as other starch. To decide whether it is absorbed as a glycogen-forming substance (presumably dextrose) or as non-glycogen-forming substances (presumably fermentation products), Klotz analyzes the fat of phloridzin-livers after starch-feeding. But why this circuitous way? The direct approach to the problem is obvious. If one wishes to learn whether a starch is absorbed as a glycogen-forming or a non-glycogen-forming material, the simple method would be to starve the animal to relative glycogen-

freedom, and then feed the grain in question. It is thus possible to determine whether one kind of grain forms more glycogen in proportion to its carbohydrate content than another kind of grain. It may be considered reasonably certain that under these conditions a high percentage of glycogen will be formed from oats; minor differences may be found between different cereals, but the results of such a direct test may be expected to rule out once for all the supposition that oats can be utilized in diabetes because absorbed in a non-glycogen-producing form. (*b*) After it has been thus proved that abundant glycogen is formed from oats, if it is further desired to know whether the glycogen-forming material is dextrose or something else, a second investigation might decide this point. It is a universal belief, which has not met serious question except from Pavy, that starch is absorbed in the form of sugar. If it is desired to know whether oat-starch is absorbed in the same form as other starch, the same methods and proofs may properly be demanded as in the case of other starch, viz., analyses of the portal blood, or something else equally direct and intelligible. (*c*) A third question is whether phloridzin disturbs these relations in any way. If it shall be found that in phloridzin poisoning, as in diabetes, differences exist between oatmeal and other meals, which are not observed in normal animals, this fact will be an interesting addition to our knowledge concerning phloridzin. But to attempt to decide these three questions all at once, and by the use of a test which competent investigators hold unreliable, is an unsuitable procedure.

The experiments of Klotz concerning the fermentability and digestibility of oats represent valuable negative evidence. Slight differences are found between oats and other grains. As would be expected, oat-starch in digestion forms sugar. Lang justly concludes that such differences between oats and other grains are inadequate to explain the benefits of the oat-cure.

There can be little question but that von Noorden is correct in holding that bacterial processes are comparatively slight in the upper part of the small intestine, and that a practically complete fermentation of the large quantity of carbohydrate administered, without symptoms on the part of the patient, is unthinkable. Best [ref. by Cohnheim and Klee] has proved that gruel is completely absorbed in the small intestine, where fermentation is at a minimum. Accordingly, all that can be left of the fermentative hypothesis is that some portion of the oats may be fermented,

and that the products thus formed may assist in the assimilation of the remainder. Two possible modes of action might be imagined, one an effect upon the pancreas or other organs, the other a loose combination of the split-products with dextrose, comparable to the synthetic compounds of Eppinger and Falk.

4. Behavior of the Kidney.

Von Noorden has paid much attention to the possibility that oats may act by rendering the kidney less permeable for sugar. Two blood-analyses of 0.14 per cent and 0.19 per cent respectively, mentioned by him in patients receiving the "cure," do not indicate any special accumulation of sugar in the body. Minkowski calls attention to the œdema which sometimes is caused by oats.

Barrenscheen, a pupil of von Noorden, mentions the increase of glycosuria that sometimes comes just after the "cure." He tried the following procedure in human subjects: injection of 20 cc. 10 per cent lactose solution intravenously; on each of the following 2 days 250 g. oats; on third day, return to mixed diet and repetition of injection. As a result of the oats, the complete excretion of the lactose was found to be delayed by 1 to 5 hours. Also, the excretion was found to be delayed in patients after infectious diseases, when the fever had gone and there were no signs of renal trouble. The work is taken to mean that slight renal changes not otherwise demonstrable, due to oats or to a preceding fever, may delay the excretion of sugar.

Blum, in an incidental blood-sugar determination in a diabetic during the "wheat-cure," found the blood-sugar not increased.

Schirokauer has lately made the only special investigation of this point. In several patients, with diabetes of different duration and severity, there was no constant effect of the oat-cure upon the blood-sugar. The general effect upon the glycosuria and acidosis was favorable, but the blood-sugar might be a little raised or lowered, or remain about the same. One case was notable, in that the patient before the "cure" was free from glycosuria with 0.182 per cent blood-sugar; during the "cure" this dropped to 0.15 per cent, and a slight glycosuria appeared; *i.e.*, the kidney became more permeable. In two patients, a "potato cure" had effects similar in all respects to those of oats.

Mirowsky has studied the water-retention which occurs in a large proportion of patients during the oat-cure. There is a sudden gain of weight amounting perhaps to several kilograms.

Generally no fluid collection is demonstrable in any cavity nor under the skin. The patient's skin is moister and better filled out; the tissues somehow retain water better. This effect, observed by numerous others, has been attributed to the oats and to sodium bicarbonate. The author tried the effects of oats and the bicarbonate in both diabetic and non-diabetic patients. The characteristic gain in weight produced in diabetic patients by oats was not produced in them by bicarbonate, and was not produced in non-diabetic patients by either oats or bicarbonate. A boy with diabetes insipidus reacted in the non-diabetic manner. Some peculiarity associated with diabetes is therefore responsible for the retention of water during the oat-cure.

It is conceivable that an increased impermeability of the kidney might improve the sugar-assimilation, and thereby the acidosis, by a little. In non-diabetics, an increase of the normally combined blood-sugar causes increased combustion and storage; accordingly, with the poorly combined sugar of diabetics, the same rule might work in less degree, and some influence permitting the blood-sugar to stand at a higher level without glycosuria might result in increased utilization. But the following considerations indicate that the renal element is of negligible importance as an explanation of the oat-cure.

(*a*) Experiments of Jeanneret, mentioned by His, showed that when diabetics receive alcoholic oat-extract as an addition to a fixed diet, the sugar-excretion is diminished on the extract-days. Others have proved that the toxic effects of oats are obtainable from extracts. But these toxic effects bring no real benefit to diabetic patients.

(*b*) Nephritis complicating diabetes may render the kidneys highly impermeable and send the blood-sugar to high figures, without benefiting the patient or relieving the acidosis.

(*c*) Numerous remedies have been tried in human and experimental diabetes, of which the effect was renal injury. The authors were encouraged by the fact that the sugar-excretion was diminished. Yet none of these remedies ever improved the diabetic condition.

(*d*) Zuelzer found oats to be not an "antagonist" of adrenalin. Adrenalin glycosuria is prevented or diminished by a long list of substances [see Chapter XIX], which have nothing in common except that they render the kidneys less permeable for sugar. It is significant that this effect was not demonstrable for oats.

(*e*) Barrenscheen's interesting experiments have not covered all the conditions. Though oats may diminish the renal permeability for sugar, diuretics ordinarily increase the excretion of sugar. Oat-œdema can frequently be overcome by theocin without the benefits of the "cure" being lost. If Barrenscheen had tested the excretion of lactose under the influence of oats plus theocin, the results might have been different.

(*f*) The blood-sugar analyses, especially of Schirokauer, positively exclude the retention of sugar in the blood in a large proportion of cases, and in any doubtful cases the increase of blood-sugar is too small to correspond to the large quantity of carbohydrate ingested.

(*g*) The fact that results nearly or quite identical with those of oats are frequently obtainable from barley, wheat, bananas, potatoes, etc., shows the renal factor to be not the explanation.

It may be admitted that in either diabetic or non-diabetic patients, especially those with sensitive kidneys, a true toxic œdema may result from oats, as described by a number of authors. But the typical water-retention, which Mirowsky found peculiar to diabetes, is scarcely of this type. It is noteworthy that this water-retention is simultaneous with a greatly improved assimilation of a greatly increased quantity of carbohydrate. It therefore corresponds to facts noted in Chapter VI, *e.g.*, the water retention observed by Voit and by Wimmer in consequence of starch-feeding in experimental animals. Also in the diabetic patients, not merely the increased quantity of carbohydrate, but the better binding of it resulting from the "cure," would be likely to cause retention of water, since the colloid sugar always tends to retain water. This result, therefore, is in agreement with the other demonstrable benefits of the "cure." It may perhaps not be invariable, since disturbing factors of various sorts may enter in.

Summary and Discussion.

It is evident that the question whether oats may be slightly more assimilable than some other cereals in diabetes, is only part of a much wider problem, concerning the widely different tendencies of different foods to produce glycosuria, not only in diabetes but even in some non-diabetic conditions. These tendencies are entirely independent of the carbohydrate content of the foods, are sometimes least in foods containing the most carbohydrate, and are shown in maximum degree by a practically

carbohydrate-free food, meat. On this basis, attention may be given to the three possible explanations of the oat-cure presented by von Noorden. 1. Oats may contain substances which influence carbohydrate metabolism in specific manner. 2. Oats may during digestion and assimilation behave differently from other foods. 3. Oats may make the kidneys less permeable for sugar.

1. Oats may contain substances which influence carbohydrate metabolism in specific manner. Against this hypothesis stand the failures to obtain any results with oat-extracts or other preparations. One of two ways, the evidence is unanimous; either it is impossible to get distinct results from any fractional part of the oats; or, if any fraction gives benefit like that of the whole oats, it is the purified oat starch. At most, therefore, this question can pertain only to a special behavior of oat-starch in digestion or assimilation, which comes under the next hypothesis. Furthermore, this hypothesis throws no light upon the general question why some foods produce so much more glycosuria than other foods, unless it be assumed that special glycosuria-producing or glycosuria-inhibiting substances are contained in all foods. The question then is why these unknown substances produce these effects, and thus we are back where we started.

2. Oats may during digestion and assimilation behave differently from other foods. Here it is possible to think of special physical or chemical properties of the oat-starch, or of some synergism between different constituents of the oats, or of fermentation products which somehow favor assimilation. The main objection to this explanation is that it is too narrow; peculiarities of oat-starch do not explain why meat causes glycosuria. There may be some degree of truth in this hypothesis, but it cannot be the main fundamental principle.

3. Oats may make the kidneys less permeable for sugar. This, as previously shown, cannot be a very important factor. It is particularly unsatisfactory for explaining the striking benefit to the acidosis and the general condition. It fails to explain the effects of other foods in preventing and in causing glycosuria.

A central question in the discussion is whether oats and other beneficial foods are absorbed in some assimilable form, different from the non-assimilable dextrose, or whether they have some action upon the body which improves the assimilation of dextrose. Positive experiments in totally depancreatized dogs would be

crucial on this point; for if such dogs utilize any starch, it is a demonstration that the absorption was in some other form than dextrose. The glycogen increase in Jastrowitz's experiments, as reported by Mohr, must at present be considered over-balanced by the entirely negative findings of Boruttau. The idea of any important absorption in forms other than dextrose is opposed by the very similar benefits obtained from a variety of carbohydrate-containing foods; the established doctrine is most probable, that these starches are absorbed as sugar. Klemperer's experiments with feeding of dextrose itself speak to the same effect.

It would seem that dogs with the type of diabetes described in Chapter X should constitute excellent material for the study of the oat-cure and related problems; and by the use of such animals the understanding of these problems should be materially advanced. Unfortunately, it has not been possible to perform oat-feeding experiments in the present investigation. The work along other lines, however, has seemed to suggest an explanation of the oat-cure. A discussion of the oat-cure at this place has been necessary because of the relation of various experiments to the amboceptor hypothesis (utilization of sugar and starch by severe diabetics, etc.). The principal evidence for the proposed explanation is given in Chapter XXII. It may be stated here, in advance of the evidence, that this proposed explanation consists in the relations between the internal and external pancreatic secretion, and the effects of intestinal influences upon the pancreas. By reason of freedom from harmful stimuli from the intestine, also perhaps by reason of a diminished labor of external secretion, and possibly by reason of a mild beneficial stimulation in a positive sense, the pancreas is able to perform its function of internal secretion more efficiently, and the diabetic condition is correspondingly benefited. The explanation agrees with facts in the literature, as follows.

(*a*) The positive glycosuric effects of meat, and the differences between different proteins, are thus comprehensible.

(*b*) The remarkable benefits reported by Funck and others from treatment of intestinal disorders in a number of diabetic patients are thus explainable. Von Noorden's discovery was made in patients with digestive troubles. Klotz's idea of the harmful effects of a putrefactive flora may well fit in here.

(*c*) It is thus possible to understand the generally beneficial effects of any purely vegetable diet. Even the assimilation of

pure dextrose after withdrawal of meat, as observed by Klemperer, becomes comprehensible. More or less difference between different cereals is not surprising, since other effects upon the intestine, *e.g.*, the laxative action of oats, are well known. It is also possible that different kinds of pure starch, through slightly different physical properties, may have slightly different effects in the intestine. In particular, one riddle becomes less puzzling, viz., the fact that the cereals must be given in a boiled form, and if baked, much of the benefit is lost. Mucilages have been used in medicine for various soothing purposes; and the slimy form of a gruel may conceivably affect the intestinal mucosa differently from the very different physical state of the cereal which results from baking.

(*d*) The suggestion was to have been made that investigation might show certain relations between the oat-cure and the external secretion of the pancreas. The fulfillment of this idea, in experiments just published by Cohnheim and Klee, has necessitated rewriting the close of this chapter. In dogs with duodenal fistulas, these authors proved that meat, through the gastric secretion excited, produces a very great flow of pancreatic juice. Bread produces a considerable pancreatic secretion; the flour or dough from which the bread is made produces very little, and oatmeal produces the least of all. Cohnheim and Klee have fully recognized the relations of their observations to the oat-cure; they point out the fact that the foods which cause the greatest activity of the external pancreatic function are the ones which give rise to glycosuria, and the foods which stimulate the external pancreatic function least are the ones which have least tendency to glycosuria; and they suggest that the internal function of the pancreas is strengthened by relieving the strain upon the external function. It is a satisfaction that my proposed suggestion concerning the external secretion of the pancreas, based upon my experiments with diabetes, has been already verified in the work of Cohnheim and Klee; and that the suggestion of these authors concerning the internal secretion of the pancreas, based upon their investigation of the external secretion, receives direct experimental support from my observations as described in Chapter XXII. These experiments from opposite sides fit together perfectly to explain the benefits of the oat-cure in a more satisfactory manner than heretofore possible.

CHAPTER X.

OPERATIVE DIABETES.

THE dog is a providentially useful animal in the study of diabetes, because of ease of handling, high general resistance, convenient anatomical relations of the pancreas, and natural susceptibility to the disease. The study of diabetes in species in which, as in man, the condition occurs sometimes spontaneously, seems to promise more than the study in other species, where no natural tendency exists. Ordway has reported the frequency of pancreatic changes in cats; but no diabetes is known among felines. The spontaneous disease, so far as we have information, is confined to man, monkeys, dogs, and horses.

Naunyn (p. 151) gives a good account of spontaneous diabetes in domestic animals. Rosenberger also mentions it. Two canine cases have been reported by Darra, and one case by Cadéac and Maignon. Preller has described the case of a horse with diabetes mellitus, with glycosuria of 2–7 per cent, and hyperglycemia as high as 0.521 per cent. Gross lesions of the pancreas seem to be the rule in diabetic animals.

Total Pancreatectomy.

Kleen (p. 135) thus summarizes the early history of experimental diabetes.

"Fully two hundred years elapsed between Brunner's original attempt at extirpation of the pancreas [1686] and v. Mering and Minkowski's discovery of the glycosuria resulting from that operation. Yet Cowley, in 1788, noted atrophy of the pancreas due to concretions in a case of diabetes, and Haller observed intense hunger after extirpation of the pancreas. Within more recent times Bouchard, in 1851, expressed his opinion of a causal connection between diseases of the pancreas and diabetes, and Lancereaux's three cases [1877] established the matter in the mind of the profession. Later, N. Senn observed several symptoms of diabetes in dogs after extirpation of the pancreas, and William T. Bull, after such an operation on a patient, observed diabetes. Both of these distinguished American surgeons, however, were concerned chiefly with the surgical features of their work, and they just missed adding a great discovery in experimental pathology to their other successes. The same fate befell Finkler and Orth, who had undertaken extirpation of the pancreas in dogs in order to observe any possible diabetic effect. They evidently failed in their purpose by not effecting complete extirpation."

From the time of Claude Bernard, complete extirpation of the pancreas was accounted impossible. Injections and ligations of the ducts were performed in order to destroy the gland; but no matter how extreme the atrophy, diabetes never resulted in such animals. Diabetes is said, however, to have been brought about by paraffin injections [von Noorden (1), p. 40]. But it is striking what advanced degenerations of the pancreas may thus be produced, without diabetes, in contrast to the relatively slight changes often found in diabetic men and animals in connection with spontaneous diabetes. Von Mering and Minkowski not only mastered the operative technique, but they also established the theory of pancreatic diabetes upon a sure and permanent basis. The many workers since that time have added some things; they have subtracted nothing. Minkowski has held his ground against many opposing doctrines, and the pancreatic theory of diabetes becomes constantly better established.

The complete extirpation of the pancreas, first practiced in dogs, was quickly extended to other animal species. The discoverers themselves thus produced diabetes in many different animals. Weintraud and Kausch studied the experimental disease in birds; Marcuse, Aldehoff, Pflüger, Velich, Loewit, and others in frogs; Aldehoff and Nishi in turtles; Caparelli in eels, and Diamare in selachians. In general, the rule holds that all species yet examined show glycosuria, or at least hyperglycemia and fatal cachexia, after complete removal of the pancreas.

The technique of total pancreatectomy in the dog is described in the original publications of v. Mering and Minkowski, in a special article by Hedon (1), and, in greatest detail, by Witzel, who performed Pflüger's operations. The longest life and the greatest freedom from shock and infection are afforded by the operation in two stages, as practiced by Minkowski and by Hedon; viz., first the removal of the entire organ except the end of the processus uncinatus brought out under the skin; then, after complete recovery, the removal of the small subcutaneous graft by a very easy operation; the dog at once develops intense, uncomplicated diabetes. Pflüger (6 and 9) insisted that Minkowski's operations were not total, and that polyphagia, polydipsia, and polyuria are the signs of incomplete extirpation. Similar claims are put forth from time to time. Ramond lately has asserted that complete extirpation is impossible without removal of the duodenum, and that the glycosuria is less intense after such com-

plete ablation. It is abundantly established that the symptoms following complete extirpation are those of intense diabetes, as described by Minkowski, and that infection, shock, or other complications explain all different results. Nebelthau, studying this question, found that fever and toxins do not change the sugar excretion of a totally depancreatized dog; but inoculation with living tubercle bacilli may do so. The result agrees with the well-known fact that sufficiently severe infection may completely prevent glycosuria in such animals (though they must be considered *diabetic* just the same). Extreme weakness likewise may inhibit glycosuria; the sugar-forming function apparently suffers. Animals may excrete sugar to death, or glycosuria may cease a little before death. Lepine (2) found that dogs depancreatized after excessively long starvation might fail to show sugar. Severe operative shock may have the same effect. Pflüger (16) mentions a dog operated upon by Witzel, which lived $2\frac{1}{2}$ days and showed no trace of glycosuria.

Various investigators have studied the length of the latent period between total pancreatectomy and the onset of glycosuria. Drennan places it at 6 to 18 hours. Lepine [(1), p. 349] presents the following table.

Beginning of glycosuria.	Number of dogs.
Between 4th and 6th hour, in.....	16
Between 6th and 7th hour, in.....	10
After 10 hours, in.....	6

Pflüger (13) discusses the subject; also Pflüger [(1), pp. 489–90] presents the following table of Bierry and Gatin-Gruzewska, concerning the beginning of glycosuria after total pancreatectomy.

Number.	Weight of dog.	End of operation.	First reduction.
1.....	10 kg.	1 o'clock	3 o'clock
2.....	14 "	4 "	5 : 35 "
3.....	20 "	1 "	3 : 30 "
4.....	14.3 "	10:30 "	3 : 30 "

Obviously, results will vary in consequence of operative trauma, the anæsthetic, and other accidental factors. The most accurate method would appear to be the removal of a subcutaneous

graft without anæsthesia in a dog previously deprived of all other pancreatic tissue, as Hedon has so often done. There is always a latent period before the onset of glycosuria or hyperglycemia. It may be interpreted as the length of time necessary for using up the stock of pancreatic amboceptor, till it falls below the necessary minimum.

Partial Pancreatectomy.

Incomplete extirpations, or accusations of them, have played an important part in diabetic literature. It will be remembered that they prevented the discovery of experimental diabetes before v. Mering and Minkowski. The claims of these authors were at first opposed by a number of operators, including de Renzi and Reale, who asserted that removal of the pancreas does not, or at least does not always, cause diabetes. Such findings are supposedly due to incomplete extirpations. Thiroloix (2) claimed a method of complete pancreatectomy which could be done in 15 minutes. The atypical results frequently recorded in his numerous publications are attributed to this incomplete method. In his paper (5) he acknowledges that a few milligrams of pancreatic tissue always remained. This accounts for his finding in one experiment a delay of 7 days before onset of glycosuria, and the mild or transitory character of the diabetes produced in some of his animals. Lesne and Dreyfus used the Thiroloix method in 19 dogs. In 11 they obtained glycosuria lasting till death; in the others, mild or absent glycosuria. Lüthje's experiments [Lüthje (3), also Embden, Lüthje and Liefmann], indicating that certain dogs burned some sugar under certain conditions, proved later to be explainable by the fact that the animals were not totally depancreatized. Pflüger (16) mentions mistakes by Küttner (a noted surgeon) and by Caparelli, dependent upon the fact that their supposedly total extirpations were not total. Turro and Py y Suñer reported pancreatectomies in 63 dogs; 37 showed sugar; the remaining 26 showed neither glycosuria nor hyperglycemia. A diet of carbohydrate, however, always caused glycosuria. The difference was largely of season; in spring and summer many dogs remained sugar-free, living 20–30, even 55–59 days; but in winter nearly all became glycosuric. An opposition was claimed to exist between sugar and nitrogen, in that the dogs showing no sugar were the ones with the greatest increase of nitrogen excretion. Borchardt, in criticizing this work, asserts that the authors have

not proved that their extirpations were complete; their remark simply that the autopsy showed total absence of the pancreas is no proof; and if removal was incomplete, the results are nothing new. Special notice, however, is due to the increased nitrogen excretion reported by these and other authors, without glycosuria.

A number of investigators have also studied the effects of intentionally incomplete extirpation of the pancreas. Von Noorden [(1), p. 40] summarizes the results of partial extirpations as follows. If one-tenth of the gland is left in functional condition, a diabetes of mild type results; glycosuria is slight and occurs only on carbohydrate diet. But if the remaining portion of the gland atrophies, the result after a time is severe diabetes, of the so-called Sandmeyer type. If more than one-tenth of the gland is left in functional condition, there is no certainty of any diabetes.

The above may be convenient for a brief statement; but the fact is that no brief statement can cover the numerous different results that have been witnessed after partial extirpation of the pancreas. Some of the authors already mentioned certainly did not leave one-tenth of the pancreas in position, yet they obtained no diabetes. Harley left only one-twentieth of the pancreas, yet there was no diabetes. The literature is very confusing, for reasons to be pointed out later.

Minkowski [(1), p. 27] found that no diabetes resulted if $\frac{1}{4}$ or $\frac{1}{5}$ of the pancreas were left in position. When smaller pieces were left, diabetes of mild type sometimes developed. In two cases, when $\frac{1}{12}$ to $\frac{1}{15}$ of the organ was left, a diabetes of the severest type ensued. From another dog was removed a piece of pancreas 25 cm. long.; the portion left was only 2 cm. long. Four days after the operation a mild glycosuria began, which became intense, and the table which accompanies shows by the D/N relations that the diabetes was total. The animal lived long in good condition. At autopsy, the pancreas fragment was not sclerotic, but showed degenerative changes. From another dog was removed about 46 g. pancreas-tissue, and about 3 g. was left. The urine that evening contained a trifle of sugar. On the next day it was sugar-free, but on the day following, intense glycosuria began, which was proved by metabolic test to be total. The dog died of peritonitis; the pancreas-remnant was found degenerated. Other dogs, in which the pancreas-remnants were not much larger and furthermore became sclerotic, showed glycosuria only in the post-operative period, and later could take 30–40 g. dextrose

or 100 g. saccharose by mouth without glycosuria. Other dogs underwent removal of all but $\frac{1}{8}$ to $\frac{1}{12}$ of the pancreas. The remnants became sclerotic, but the animals showed no diabetes, only alimentary glycosuria. Removal of the sclerotic remnant in such cases brought on typical diabetes. Minkowski (pp. 40 ff) found that grafts of pancreas 5 or 6 cm. long transplanted under the skin of the abdomen serve to prevent diabetes. A dog with a graft $3\frac{1}{2}$ cm. long showed intense diabetes, but the wounds healed well; at autopsy the remnant was found atrophied. Minkowski (p. 97) has also observed the rapidly fatal cachexia in some dogs after partial pancreas-extirpation; he considers it unproved whether the condition is not perhaps due to digestive disturbance. On page 32, he correctly calls attention to the importance of the effects of partial extirpation for the theory of diabetes; and notes it as a remarkable fact, that the intensity of the diabetes following partial extirpation stands in no fixed relation with the size of the gland-remnant nor with the intensity of the anatomic changes in it.

Hedon was one of the early workers with partial extirpations. He devised independently the method of subcutaneous grafts, and found in some cases that $\frac{1}{30}$ of the pancreas may suffice to prevent glycosuria. He was one of those to prove that the pedicle of the subcutaneous graft may be ligated after healing is complete, and diabetes still remain absent. His experience with the cachexia which sometimes follows partial extirpation, caused him to apply the name of "diabetes without glycosuria." The term is a commendable one, for it calls attention to the distinction between diabetes and glycosuria.

Thiroloix was another early worker. The 15-minute operation which he devised consists essentially in tearing out the pancreas with the hands. The vessels thus broken bleed little. It is the boast of the author and his pupils [as Lesné and Dreyfus (1)] that no instruments at all and only one or two ligatures are necessary. Thiroloix's researches are described by Pflüger (1), beginning page 466; and on page 472 the method of operation is described. Extirpations by this method, even when called "complete," are of course not complete. But Thiroloix's work possesses value as a study of nearly complete extirpations of the pancreas, a subject which has been too much neglected.

Thiroloix (5), after starving dogs for 5 days before operation, found that the result was polyuria and increased nitrogen excretion,

without glycosuria. By feeding a few grams of meat every 8 hours, an intermittent glycosuria could be produced, when a few milligrams of pancreas-tissue were present. If a few centigrams were left, glycosuria occurred only on carbohydrate diet. In other publications, when operations were performed without preliminary starvation, he reported that glycosuria might sometimes be delayed as long as 7 days. Thiroloix (3 and 6) made subcutaneous grafts which secreted digestive juice and prevented diabetes, even after their pedicles were cut. In (3) he reports an important observation [quoted also by Minkowski (1), p. 38]; viz., a subcutaneous graft prevented diabetes for 21 days; diabetes then suddenly came on, but the graft continued to secrete pancreatic juice as before.

Sandmeyer (1 and 2) devoted himself more specifically than others to the study of the late diabetes which comes on after slow atrophy of a small remnant of pancreas left in the abdomen. For that reason, and for the sake of convenience, we may accept Pflüger's designation of this type as "Sandmeyer diabetes," although Sandmeyer was not the first to observe delayed diabetes. Sandmeyer's first paper is concerned chiefly with total extirpations, and there is very brief mention of the partial operation. In the second paper, two dogs are described. In the first, a piece of pancreas 24 cm. long, weighing 28 g., was removed, and 3 cm. of the end of the processus uncinatus was left, separated from the bowel, and furthermore with the principal vessels of supply ligated. Glycosuria appeared 4 months after operation, and the animal died about 2 months later. In the second, the extirpated piece weighed 15 g.; the remnant was about 3 cm. long. It was at the splenic end, not communicating with the bowel, and its vessels were not tied. Glycosuria came on 13 months after the operation, and death occurred 8 months thereafter. The demonstration of diabetes after such long delay, and the prolonged metabolism experiments carried out on these dogs, are justification for giving Sandmeyer's name to this type of the disease.

The work of de Renzi and Reale was called into prominence especially by Pflüger (21 and 22), in connection with "duodenal diabetes." The most notable fact is that they succeeded in producing in one dog a definite and prolonged, though very mild diabetes, with the pancreas intact. They themselves could not reproduce the condition, and Pflüger tried vainly in many ways to imitate it. The work is now generally disbelieved or forgotten,

and even Pflüger suggested that some ill-disposed individual had perhaps put glucose in their dog's urine. De Renzi and Reale (2) observed permanent diabetes in one dog after removal of seven-eighths of the pancreas; evidently the fragment communicated with the bowel, for it was found in healthy condition at autopsy. The lack of an explanation has been the sole ground for skepticism concerning these interesting and important observations.

Pflüger [(1), p. 466 ff] describes the transient glycosuria that may follow partial extirpation, injection of the ducts, and other operations upon the pancreas. He failed, however, to distinguish between diabetes and simple traumatic glycosuria. Pflüger (p. 473) also describes Lüthje's technique, which consisted in removing all of the pancreas except small shreds, and then burning these with the Paquelin cautery. These were the extirpations which, represented as "complete," gave rise to erroneous claims concerning the power of sugar-combustion in totally depancreatized dogs, in experiments with cold and muscular exercise.

Pflüger (13) devoted a long and able paper to an argumentative and experimental attack upon the Minkowski doctrines. As is well known, Minkowski has always maintained the essential rôle of the pancreatic tissue itself in the prevention of diabetes. Pflüger assailed this position repeatedly and unsuccessfully, at first considering the phenomena entirely nervous, and later emphasizing the importance of the nervous regulation of the pancreas. The above paper is devoted to this latter argument. Pflüger's fundamental conception here — namely, that nervous influences must be important in diabetes, and that human cases plainly indicate such an etiology — is unquestionably correct, and incidentally is not opposed to anything that Minkowski has maintained. The Sandmeyer type of diabetes, coming on in consequence of atrophy of pancreatic tissue, long after the immediate effects of the operation, was essentially the thing which forced Pflüger to admit the indispensable function of the pancreatic cells themselves. Pflüger imagined other possibilities, such as long-continued irritation by ligatures, as the cause of the diabetes. If diabetes could be produced without atrophy of the remnant, his contention against Minkowski might be made good. He therefore, at the outset of this work, had Witzel remove three-fourths of the pancreas from two dogs, leaving the remnant in communication with the duct, so that it did not atrophy. He observed the animals for 11 months,

and tested their tolerance for sugar. There was no diabetes nor other disturbance, and the assimilation of sugar is said to have been normal. Pflüger admits the difficulty of accurate alimentary tests. If he had used the convenient and accurate subcutaneous test, he would have found the tolerance of his dogs reduced. But he considered his attempt in this direction a failure, and so he wandered off into the error of "duodenal diabetes," the conception that the duodenal nerve-plexus governs the pancreas, and that extirpation of the duodenum therefore causes diabetes. In those two partial extirpations at the outset of this work, Pflüger was like Napoleon at Acre. If he had removed just a little more pancreatic tissue, the diabetes which he so earnestly desired would have been his, and the history of diabetic research would have been changed. In Pflüger's hands, such a form of intense diabetes, with a considerable piece of intact pancreatic tissue still present, would have been a tremendous weapon against the Minkowski school. Minkowski's position is right; but so also was Pflüger's right in many respects. Minkowski dealt with definite anatomical conditions, and he proved his case. Pflüger struggled with the difficulties of neurological physiology and pathology. Broadly and fundamentally he was right, but he never proved it. His "duodenal diabetes" found some supporters, but Waterloo came when Minkowski (7) exhibited a dog in perfect health with full carbohydrate tolerance after complete removal of the duodenum, and the same dog subsequently after removal of the pancreas developed typical diabetes. Pflüger's later writings show the bitterness of defeat, and he died seeing the Minkowski school victorious and dominant. The removal of a few grams more of pancreatic tissue in 1906 would have changed the situation. It would not have overthrown Minkowski, but it would have armed Pflüger. The result, followed up as Pflüger would have followed it up, would have made the contest a draw, which is today the right decision. The just relation of Minkowski and Pflüger is not as victor and vanquished, but as two men who saw two different sides of diabetes. The one had a more definite problem, and proved it. The other's task was more difficult; he labored just as faithfully and ably, but the proof escaped him. To have formed many erroneous hypotheses was inevitable in such work as Pflüger's. But future study of diabetes will confirm an opinion already justified, that Pflüger's conception of a nervous basis of diabetes stands on the same level of truth with Minkowski's conception of

an anatomical basis of diabetes. They fit together into a perfect whole.

Allard [(3), p. 395] mentions one of his dogs with a subcutaneous graft, which after several weeks became diabetic. The diabetes at first was mild, later became maximum, with acidosis, so that no change in the D/N ratio followed the extirpation of the graft.

Minkowski [(6), p. 399] describes two dogs with the processus uncinatus transplanted under the skin. One had an abnormally small vascular supply to the graft, but the graft was twice as large as in the other dog, and secreted 7 times as much juices. The juice of both grafts had the normal digestive properties. The small graft of the second dog atrophied, but there was no diabetes for two months, and then only a trifling glycosuria (about 1 g. daily excretion; D/N = 0.1–0.2). But the dog with the large, actively secreting graft quickly developed adiabetes of almost the same intensity as that seen after total extirpation (D/N = 2–3).

Tiberti and Franchetti (1 and 2) found $\frac{1}{4}$ or $\frac{1}{5}$ of the pancreas to be always sufficient to prevent diabetes. In one case they left the remnant in communication with the duct, and there was no diabetes. Partial extirpation resulted in diabetes only when nearly the whole pancreas was removed.

The recent observations of Thiroloix and Jacob deserve special notice because of their very interesting nature. Thiroloix and Jacob (1) began with the assumption that total removal of the pancreas cannot be expected to reproduce accurately the type of diabetes seen clinically, in which little if any pancreatic tissue is destroyed. In order to approach the human condition as nearly as possible, they undertook extirpations of the greater part of the pancreas, leaving the remnant in communication with the duct. The animal's nutrition is thus better maintained, and such operations seldom cause death. They have had positive results with five dogs, and one protocol is presented as typical of all the rest. This was an 8-kilo dog, whose pancreas was ligated 1 cm. above and 1 cm. below the main duct. The portion included between these ligatures is said to represent one-fifth of the gland. This portion was left; all the rest of the pancreas (weighing 21 g.) was removed, using the Thiroloix method of tearing out. Thus, a remnant as large as a walnut was left surrounding the duct. By the next day, the animal appeared well, and glycosuria set in. This glycosuria continued, varying from 8–10 per cent; and as the daily urine was 300–500 cc., the sugar-

excretion on meat diet thus amounted to 24–50 g. per day. The animal's general appearance remained normal. The feces were soft, normally colored. Under the microscope they showed many muscle-fibres, but without nuclei or striation. Fat-droplets and crystals of fatty acid were present. These authors (2) claim to have removed all but 10 g. of pancreatic tissue in an 8-kilo dog, then to have removed half of this, leaving 5 g., and the dog became glycosuric after 4 days. In their third paper, diabetes is described with a remnant of one-eighth of the gland. At autopsy not only the pancreas remnant, but also the liver, thyroid, adrenals, hypophysis, and ovary or testis were found normal. Their fourth paper is a general summary of their results, to the following effect. (A) Complete extirpation of the pancreas causes an acute, quickly-fatal diabetes. (B) Nearly total extirpation, with ligation of ducts and consequent atrophy of the remnant, gives rise at first to emaciation without glycosuria, then to a wasting glycosuria. Sometimes the emaciation of the primary stage ceases, and the animal becomes fat before becoming diabetic. (C) The nearly total extirpation of the pancreas with preservation of a *special fragment* ($\frac{1}{5}$–$\frac{1}{6}$) surrounding the main duct, gives rise to forms of diabetes distinguished by the absence of emaciation and the long course of the disease. The animal can utilize some glucose, and can assimilate fat up to 80 per cent. By this technique, two forms of diabetes are produced: (1) a rapid form in which glycosuria is constantly present and progressive, acetonuria exists, and death occurs from marasmus in 3 to 6 months; (2) a slow form, in which the animals live 13 to 18 months. After a transient loss of flesh, they gain weight and appear like normal animals. For the first 5–8 months, there is nothing but a strong tendency to alimentary glycosuria; even a very small quantity of carbohydrate food gives rise to marked hyperglycemia and glycosuria. The glycosuria is absent on meat diet. Long-continued carbohydrate feeding finally gives rise to incurable glycosuria and emaciation. At autopsy, the pancreas-remnant appears in good condition. Other viscera are normal, except the liver, which may be normal, enlarged, fatty, or sclerotic. The authors therefore assert that a simple modification of the technique of pancreas-extirpation permits production of types of diabetes resembling the clinical "diabète gras."

Thiroloix and Jacob have thus contributed an interesting confirmation of the discoveries of de Renzi and Reale, Minkowski,

and several others, that diabetes of severe grade may occur when a considerable fraction of pancreatic tissue is present and actively performing its external function. The original discovery belongs to de Renzi and Reale. Minkowski contributed the only exact histological study of the pancreatic tissue under these conditions. Thiroloix and Jacob have added a number of observations or conclusions which are, in my opinion, erroneous. Most of the points involved will be considered in detail later. The statement that diabetes occurs when the remnant is $\frac{1}{5}$–$\frac{1}{6}$ of the pancreas is, in my experience, incorrect, and probably based upon inexact estimation of the size of the remnant. The assumption that the remnant must consist of a special portion of the pancreas, and that it must secrete into the bowel, is contrary to the experience of former authors who have observed intense diabetes when the remnant consisted of the end of the processus uncinatus, and when its secretion was discharged externally. In reporting the pancreatic tissue normal, Thiroloix and Jacob have failed to confirm the suggestive microscopic findings of Minkowski. In the production of this type of diabetes, Thiroloix and Jacob have also laid emphasis upon the method of operating, viz., by tearing. Their work first came to my attention after all my experiments were ended, so that there has been no opportunity to make a definite test of this method; but the experiments concerning the effects of local trauma and nervous or vascular injuries, as presented in Chapter XVII, seem to me to rule out the operative method as a factor in producing the results. In general, therefore, the statements of previous writers are more exact than those of Thiroloix and Jacob; and the contribution of the latter is limited to one new point. This is the influence of diet; viz., the fact that a dog with a pancreas remnant of suitable size, and without glycosuria on meat diet, may, by sufficiently prolonged carbohydrate diet, be reduced to a condition of severe diabetes, in which sugar-freedom on meat diet is no longer possible. Control experiments would be desirable, *e.g.*, concerning the length of time such dogs may remain free from diabetes when not subjected to carbohydrate diet. But such a lowering of tolerance, apparently due directly to the diet, and certainly not associated with any gross degeneration of the pancreas remnant or impairment of its external secretory function, is a new observation in experimental diabetes, which raises the work of Thiroloix and Jacob to a position of high importance. This point will be further discussed in Chapter XIII.

My own production of this type of diabetes came about in the earlier part of this investigation, while following one of the primary lines of the plan. This was to try the effects of various supposed diabetogenic agencies upon animals predisposed to diabetes. This predisposition was to be produced by the removal of various fractions of the pancreas. The very first operations revealed the fact that diabetes occurs when considerable amounts of normal-appearing, secreting pancreatic tissue remain in the body. This result seemed at first astonishing, and appeared as a new discovery. These observations were several months before the first publication of Thiroloix and Jacob, which also, as previously stated, remained unknown to me till a few months ago, after all experiments were ended. But a search of the literature showed that the observation had been made before, with pancreas-remnants of the same size as in my experiments. But none of the previous investigators have found an explanation why diabetes may occur under these conditions, and why it may sometimes remain absent when the pancreas-remnant is much smaller. This explanation seemed to be the most vital question pertaining to the subject, and one possessing the highest theoretical and practical importance. It has therefore been made one of the principal objects of this investigation, and will be followed in later chapters. The present chapter is devoted only to the description and methods, and the typical and atypical results, of pancreatic operations in dogs, when complicating procedures are avoided, and the remnant is left in its normal connections with blood-vessels, nerves, and ducts.

Anatomy.

Only a few points concerning the anatomy need be reviewed. The dog's pancreas occupies essentially the curve of the duodenum, and is inclosed between the two leaves of the mesentery. Both duodenum and pancreas are very freely movable and easily accessible as compared with the human organs. The prevalent nomenclature is that of Pflüger, which divides the pancreas into three parts, viz., the *body* and two *processes*. The *corpus pancreatis* is the portion closely applied to the duodenum, from which the ducts pass into the duodenum. The younger the dog, the more loosely is the body of the pancreas bound to the duodenum, and the more easily can the two be separated. At the upper end of the body, the pancreas makes an abrupt turn, and sends off a long arm toward the spleen. This (the tail of the gland in human

anatomy) is the *processus lienalis*. At the lower end of the body, the pancreas leaves the duodenum, and passes caudalward for several centimeters. This portion is the *processus uncinatus;* it is the part used for making a subcutaneous graft, because of its free mobility and its independent blood-supply. The size and shape of the pancreas, and the length of its processes, are widely variable. The organ may be very short and thick, or very long and thin. The size varies with the size of the dog, but also independently. Occasionally one will see a small dog which has as large a pancreas as another dog twice its size. An extreme illustration was Dog 107, where the body-weight was 8 kilos, and the pancreas could not have weighed over 10 g. I have conducted no definite experiments on the subject, but have received the impression that variations in the dextrose tolerance corresponding to these variations in the weight of the pancreas do not exist. Diabetes is not more easily produced in an animal with a small pancreas than in one with a large pancreas. Though the actual size of the pancreas-remnant may be very different in the two cases, yet it must represent always the same approximate fraction of the gland. Rightly or wrongly, it has seemed that the resulting diabetes is generally more satisfactory in an animal with a large pancreas; possibly it is merely that a large, vigorous pancreas goes with excellent constitutional strength and vitality. The facts in dogs do not support the idea that a naturally small pancreas may predispose a patient to diabetes.

The blood-vessels of the pancreas of importance in operating are the splenic and the pancreatico-duodenal. The splenic vessels lie close to the processus lienalis, and supply it by several branches. The remainder of the gland is supplied by the superior and inferior pancreatico-duodenal vessels. The superior pancreatico-duodenal vessels approach from above in the form of single large stems. The inferior pancreatico-duodenal vessels approach from below, and divide into a *ramus duodenalis inferior* and a *ramus pancreaticus inferior*. Typically, the former should pass by the processus uncinatus, perhaps giving off a small branch or two to it, and supply the duodenum; while the latter should enter as a stout artery and vein into the tip of the processus uncinatus, and become buried in its substance. These latter are the vessels which constitute the pedicle and furnish the blood-supply when the processus uncinatus is transplanted under the skin. As a matter of fact, wide variations are found in these

rami. Either of them may be large or small, single, double, triple, or absent. The superior and inferior pancreatico-duodenal vessels lie partly between pancreas and duodenum, partly buried in the substance of the pancreas, giving off branches at right angles to both organs. They meet and fuse in a rich anastomosis. Throughout the entire pancreas, the anastomosis is so free that collateral circulation is abundant. So far as the pancreas is concerned, any vessel may be ligated at any point with impunity, provided the circulation from the other direction is not blocked. But inasmuch as vessels may sometimes thrombose, from injury while being dissected out from the pancreas substance, it is wise when possible to save every vessel except the branches supplying the actual portion removed.

The ducts of the dog's pancreas are described by different authors as from two to four in number. There are regularly two ducts, which communicate with the general duct-system of the gland. The one or two additional ducts which may be present sometimes do not communicate with the main duct-system. Continually and repeatedly throughout the literature, the chief pancreatic duct of the dog is called the duct of Wirsung, and an earnest protest against this incorrect nomenclature is in order. The duct of Wirsung is the duct of the ventral anlage, and therefore is always recognized by its relation with the bile-duct. In man it happens to be the chief duct. The canal of the dorsal pancreatic anlage is the duct of Santorini. It is always at some distance from the bile-duct, and in the dog it is the chief duct. To attempt to apply the name of Wirsung to the chief duct in the dog makes inexcusable confusion. Anatomists may settle the matter by a technical nomenclature (Revell suggests ductus hepatopancreatis or ventropancreatis for the duct of Wirsung, and ductus dorsopancreatis for the duct of Santorini). But in surgical use, if one means main duct it is sufficient to say main duct, and if one means lesser or smaller or accessory duct, it is sufficient to say so. The lesser or accessory duct, or ductus Wirsungianus in the dog, is a small white structure, slightly difficult to find, which opens either into or near the bile-duct. This small duct passes into the substance of the pancreas, and there joins the chief duct, in such manner that the two form a bridge over the pancreatico-duodenal vessels. The main duct is formed in the body of the gland by the union of the main stems from above and below, and opens independently on a papilla 2 to 5 cm. below the lesser duct and

bile duct. For the smaller one, the bile-duct is the chief landmark. Near the larger one generally lies one of the largest branches given off by the pancreatico-duodenal vessels to the duodenum, and this vascular landmark is easily seen. Supernumerary ducts when present are small white threads, which may lie close to the lesser duct, though the commonest position is somewhere between the two regular ducts. Gentle blunt dissection quickly locates the general position of a duct. Elsewhere, the pancreatic tissue is easily pushed back from the duodenum; but it clings closely about a duct, anchoring the gland to the duodenum, while concealing the duct itself from view. The main duct is very easily found and identified. Pressing back the pancreas-tissue and generally a little fat in the region of the vascular branch above mentioned, one sees this duct as a flattened, shining white band sinking into the pinkish wall of the duodenum, nearer the posterior than the anterior surface of the pancreas.

Operation.

In contrast to the total, the partial extirpation of the pancreas is an easy operation, which can be done within half an hour. Only operator and anæsthetist are needed. Almost any average sort of a dog may be used, but those weighing between 5 and 12 kilos are generally preferable. Very small dogs generally will not endure diabetes long; and in over-large dogs the mortality is higher. Mere puppies are unsuitable, though a 10- or 11-month animal is sometimes a splendid subject. Senile animals are generally disappointing. Excessively fat animals are worst of all; the operation is not only difficult, but the dog is liable to die without visible cause. Fancy breeds generally lack strength. The ideal dog is a sturdy, short-haired mongrel, or a Boston terrier, or a large fox-terrier, or some mongrel with bull-dog blood. The real bull-dog with tremendous musculature and supposedly unlimited resistance often bears the diabetic operation badly. Collies, hunting-dogs, and very long slim animals have been unsatisfactory in my experience.

Various lengths of preliminary starvation have been tried; one day is best. The incision is generally in the mid-line. Operative details may be omitted, except the suggestion that the handle of a hemostat may be found useful in freeing the pancreas; the edge of the ring of the handle takes hold of the pancreatic tissue without tearing it or its vessels. Dissection should be reasonably clean,

but the excessively scrupulous care to remove every visible particle, as in total extirpation, is unnecessary. Strict surgical methods may also be relaxed if desired, in the direction indicated by Thiroloix. In some operations I have endeavored to ligate even the smallest blood-vessels before dividing them, and to dissect as carefully as possible. In other operations, the method described in the protocols as "rough" has been used; the pancreas has been stripped out rather rapidly with the handle of a hemostat, the smallest vessels being broken without ligature. Gauze-pressure on the denuded area as the dissection advances keeps the field clean, and by the time the operation is finished oozing has ceased. The results as respects diabetes are identical. From the standpoint of mortality, rapidity of operating gives better results than excessive technical care. The mortality should be low. Most of the deaths in my series are explainable by the improvised operative environment; one long series of infections ceased promptly when the room was fumigated.

In my operations, all pancreatic tissue removed has been saved for weighing. A remnant of the desired size is left about one of the ducts. When the operation is complete, a piece of the excised tissue is trimmed as accurately as possible to imitate the remnant; the weighing of this piece gives the estimated size of the remnant. In dogs dying shortly after operation, it can be shown that this method of estimation yields accurate results. Mere guesses of the size lead to error; and when the dog has lived several days or longer, the weighing of the remnant at autopsy is unreliable, owing to inflammation, hypertrophy, and other changes. The most important final step, from the surgical standpoint, is to cover the pancreas-remnant and all the denuded surfaces about it with omentum. A few light sutures may be used, but the simple draping of the omentum about the operative field is generally sufficient. In this manner all troublesome adhesions are avoided, and it is possible to operate repeatedly upon the pancreas-remnant or its neighborhood, as easily as if there had been no previous operation.

Results.

Human diabetes can be only vaguely divided into severe and light cases. In dogs, it is possible to govern conditions accurately and draw lines sharply. The following classification has been used:

Diabetes gravis { Permanent. / Transient. } Diabetes levis { Permanent. / Transient. }

Diabetes gravis is the condition in which a dog excretes sugar on meat diet (generally also on starvation). Usually it is permanent, but with a pancreas-remnant of suitable size it may disappear within a week or two. The animal then represents a case of permanent *diabetes levis;* that is, he excretes sugar on starchy diet, but not on meat diet. Permanent diabetes levis is a relative term, as will be more fully explained in Chapter XIII.

With a larger pancreas-remnant, the animal after operation will excrete sugar only on carbohydrate diet. In this case, after a period of weeks or months, the glycosuria frequently passes off, and the dogs can live on bread and even take considerable sugar without glycosuria. Such cases, therefore, are transient diabetes levis. With still larger remnants, diabetes is absent but the sugar-tolerance is reduced. I have not studied remnants smaller than one-fourth of the gland. But, contrary to what has been supposed, such a reduction of pancreatic tissue invariably causes a demonstrable lowering of sugar-tolerance. The operation should be a simple reduction of pancreatic tissue, without ligation of ducts or any other of the disturbances to be discussed later. The best method of testing the tolerance is that of subcutaneous injection. In Chapter VI, I presented records (especially Dog 17) which show how marked may be the lowering of tolerance when a dog has only one-fifth of his pancreas. And yet there is no diabetes. The supply of pancreatic amboceptor is reduced, but it is not reduced below the actual requirements of metabolism. In *diabetes levis*, the supply of amboceptor is still further reduced. It is reduced below the requirements of rich carbohydrate metabolism, but not below the requirements on meat diet. The typical case of *diabetes gravis* represents a reduction of pancreatic amboceptor below the *minimum* requirements of metabolism; the animal cannot nourish himself on any sort of diet without glycosuria, and generally excretes sugar even on starvation.

The largest piece of pancreas that can be depended upon to permit *diabetes gravis* in practically every case is one-tenth of the gland. When one-ninth of the gland is left, diabetes gravis generally results. When one-eighth is left, permanent diabetes gravis sometimes results; but frequently the condition is only transient *gravis* or permanent *levis*. When one-sixth of the gland is left, transient diabetes levis is generally what is obtained. Atypical results in either direction are possible but infrequent.

To avoid prolix details, the records generally do not attempt to

describe the exact shape of the remnant. A slight question naturally arises whether the portion of tissue immediately about the main duct has less anti-diabetic activity than other parts of the gland. In pursuance of a plan early adopted, this question has been satisfactorily answered in the negative by modifications in the shapes of many different remnants. Remnants have been left communicating sometimes with a lesser duct, more frequently with the main duct. The remnant may be a compact clump closely surrounding the duct, or it may be trimmed long and narrow, so as to extend a considerable distance in either direction. By suitable modifications, and by taking advantage of anatomical variations, practically the entire body of the gland has been tested in the form of differently-placed remnants in different animals. Also, elongated remnants communicating with the lesser or greater duct have been made to extend some distance into the processus lienalis or uncinatus. As previously mentioned, other authors have obtained diabetes by leaving the end of the processus uncinatus. Hardly anything is left untried therefore but the end of the processus lienalis, and the conclusion is justified that results are not due to any lack of anti-diabetic power in any one portion of the pancreas.

The urine in later stages has generally had the intensely heavy, sweetish odor characteristic of diabetes. Acetone excretion in these stages has been very heavy as indicated by qualitative tests; quantitative determinations have not been made. The ferric chloride reaction has been invariably absent. No tests for β-oxybutyric acid have been made.

Experiments.

A number of animals used for special purposes will be reserved for later chapters. A sufficient series will be presented here to illustrate general conditions. The experiments will be grouped under the divisions of

1. Permanent diabetes gravis.
2. Transient diabetes gravis.
3. Diabetes levis.
4. Miscellaneous experiments.
5. Other pancreatic disturbances.

The subject of the morphological pathology, and especially the microscopic alterations, will be treated later in a special chapter.

1. Permanent Diabetes Gravis.

Dog 19; female; age 3 years; weight 7900 g.

February 7, removal of pancreatic tissue weighing 27.8 g. Remnant communicating with lesser duct estimated at 0.5 g.

Owing to the large proportion of tissue removed, digestion was somewhat impaired. The course of the diabetes was practically the same as in dogs with far larger remnants; that is, the mere size of the remnant does not influence the course of the disease in any absolute manner either for good or for bad. If anything, the sugar excretion was less with the smaller remnant.

Starvation which began March 1 showed that the excessive tissue-destruction of the totally depancreatized dog is here absent, though the pancreas-remnant is so small. The results of the dextrose injection of March 18 have been noted in Chapter VI. The dog had apparently no more tolerance for injected dextrose than a totally depancreatized animal.

Dog 20; female; age 11 months; weight 5635 g.

December 7, removal of pancreatic tissue weighing 14.7 g. The remnant about the lesser duct was guessed approximately at 3 g.; at autopsy it weighed 2.7 g. The downward course of the disease was well illustrated, glycosuria being mild and irregular at first, later constant and intense; acetone and sweet odor being absent from the urine at first, later heavy. The metabolism experiments were described in Chapter VI.

Dog 49; female; age 2 years; weight 5900 g.

May 22, removal of pancreatic tissue weighing 14.8 g. Remnant communicating with lesser duct estimated at 0.2 g.; remnant about main duct estimated at 0.5 g. The diabetes was severe.

Dog 64; female; age 2 years; weight 10,700 g.

June 7, removal of pancreatic tissue weighing 22.2 g. Remnant communicating with lesser duct estimated at 2 g. The metabolism experiments were discussed in Chapter VI. The downward course is illustrated by the feeding of eggs on June 25 and August 14. On June 25, after starving till sugar-free, a dozen eggs caused no glycosuria. On August 14, after starving sugar-free, a dozen eggs caused a glycosuria of 9.1 per cent.

Dog 90; male; adult; weight 12,425 g.

September 18, removal of pancreatic tissue weighing 16.7 g. Remnant communicating with main duct estimated at 1.4 g.; also, processus uncinatus transplanted subcutaneously estimated at 2.4 g. The intense diabetes which resulted under these conditions is exceptional, and perhaps related with the special inflammatory changes, to be more fully mentioned in Chapter XXI. It may be concluded that the processus uncinatus has no greater power to prevent diabetes than the body of the gland. The conclusion is in agreement with the observations of Allard and Minkowski, of diabetes when a considerable fragment of processus uncinatus was present under the skin.

Dog 91; male; age 1 year; weight 12,900 g.

September 20, removal of pancreatic tissue weighing 21.6 g. Remnant communicating with main duct estimated at 0.9 g. End of processus uncinatus transplanted subcutaneously estimated at 3.3 g. Diabetes failed to occur, as is usual when the pancreas-remnants are so large.

Dog 99; male; age 1½ years; weight 12½ kilos.

September 29, removal of pancreatic tissue weighing 19.9 g. Remnant communicating with lesser duct estimated at 1.5 g. Processus uncinatus transplanted subcutaneously estimated at 4.1 g. Diabetes remained absent. This is another case showing that the case of Dog 90 is exceptional.

Dog 130; male; age 3 years; weight 11,900 g.

November 1, removal of pancreatic tissue weighing 24.7 g. Remnant communicating with main duct estimated at 0.5 g. Diabetes of rapidly fatal course ensued. The urine record was as follows.

	Quantity, cubic centimeters.	Dextrose, per cent.
Nov. 2	290	0
Nov. 2 (noon)	95	2.1
Nov. 3	320	10.
Nov. 4	415	10.
Nov. 5	375	4.8
Nov. 6, in bladder at autopsy	....	2.4

No cause for death was found. The pancreas remnant appeared healthy, and weighed 1.1 g.

Although the pancreas remnant was so small, there is observed the late onset of glycosuria, characteristic of this type of diabetes. Whenever urine-specimens are obtained at sufficiently short intervals, it is regularly found that glycosuria does not begin for 24 hours or longer. That is, since the remnant can supply a small quantity of pancreatic amboceptor, the stock is not used up quite so soon as after total extirpation.

Contrary to general notions regarding glycosuria following operations about the pancreas, I have had practically no post-operative glycosuria from my operations. Glycosuria comes on only with the beginning of true diabetes.

Dog 66; female; age 3 years; weight 13,120 g.

August 8, removal of pancreatic tissue weighing 27 g. Remnant communicating with main duct estimated at 2.7 g.; remnant about lesser duct estimated at 0.25 g. Here as usual two pancreas-remnants acted the same as a single remnant of equivalent weight. The slow onset of glycosuria is again indicated by the following urine record.

	Quantity, cubic centimeters.	Dextrose, per cent.
Aug. 9	110	0
Aug. 10, a.m.	400	0.44
Aug. 10, p.m.	260	1.5
Aug. 11	....	Heavy
Aug. 12	....	Heavy
Aug. 13	....	Heavy
Aug. 14	....	Heavy

Prolapse of a coil of intestine through angle of wound. Operative repair. Death from peritonitis. Autopsy urine contained 2.4 per cent sugar. Pancreas-remnants together weighed 5.4 g.

Dog 88; female; adult; weight 7 kilos.

September 13, removal of pancreatic tissue weighing 11.9 g. Remnant communicating with main duct estimated at 0.9 g. Scattered remnants without duct-communication estimated at 0.75 g. Urine record as follows.

September 14, no urination.
September 15, 100 cc., sugar-free.
September 16, 100 cc., 3.8 per cent sugar.
September 17, 740 cc., 2.2 per cent sugar.
Thereafter, permanent heavy glycosuria.

Investigators sometimes have reported that "total" pancreatectomy has produced no diabetes. Their failure has been attributed to small fragments not removed. In this dog, the scattered fragments along the blood-vessels were larger than the average operator would leave accidentally. These fragments failed to prevent diabetes. The onset of glycosuria was late; but it turned out to be a true *diabetes gravis*.

Dog 127; male; age 1 year; weight 6860 g.

October 28, removal of pancreatic tissue weighing 21 g. Remnant about lesser duct estimated at 0.6 g.; duct cut between ligatures.

Here the amount of pancreatic tissue left was more than anybody should leave accidentally. All communication with the bowel was cut off, but abundant blood-supply was preserved. The result shows that a small remnant not communicating with the intestine does not necessarily prevent diabetes gravis. Urine-record:

October 29, no urination.
October 30, 125 cc., 7.3 per cent sugar.
October 31, 70 cc., 12.1 per cent sugar (fed milk).
November 1, 175 cc., 14.6 per cent sugar (fed bread-and-meat).
November 2, 575 cc., 8.1 per cent sugar (fed bread-and-meat).
November 3, 1015 cc., 4.1 per cent sugar (fed meat).
November 4, 500 cc., 1.1 per cent sugar (fed meat).
November 5, 250 cc., 3.0 per cent sugar (fed meat).
November 6, 200 cc., 6.1 per cent sugar (fed meat).
Permanent diabetes gravis.

Dog 149; male; age 1½ years; weight 12 kilos.

November 16, removal of pancreatic tissue weighing 26.2 g. Remnant communicating with main duct estimated at 1.5 g. Urine-record:

Date.	Cubic centimeters.	Sugar, per cent.
Nov. 17	230	0
Nov. 18	285	2.4
Nov. 19	340	9.1
Nov. 20	90	15.4

Found dead. Autopsy shows no cause. Liver fatty; other viscera negative. Pancreas remnant appears normal; weight 2.7 g.

The intense diabetes and rapidly fatal cachexia are evident from the record. Such cases are presumably due to disturbance not merely of the carbohydrate function of the pancreas, but of another function, the loss of which produces the cachexia seen always after total pancreatectomy. In most dogs made diabetic by the method which I have used, this cachexia remains absent.

Dog 170; male; age 2 years; weight 9675 g.

December 14, removal of pancreatic tissue weighing 19 g. Remnant communicating with main duct estimated at 2.6 g. The following record shows the intense diabetes, which in this case resulted when $\frac{1}{8}$–$\frac{1}{9}$ of the gland was left in position.

Date.	Urine, cubic centimeters.	Sugar, per cent.
Dec. 15	70	2.2
Dec. 16, a.m.	90	1.4
Dec. 16, p.m.	100	14.6
Dec. 17	175	14.6
Dec. 18	70	20.8
Dec. 19	310	12.1
Dec. 20	110	12.2

Such glycosuria continued till death, in consequence of a secondary operation, on December 25.

Dog 178; female; age 2 years; weight 9300 g.

December 29, removal of pancreatic tissue weighing 20.4 g. Remnant communicating with main duct estimated at 2.2 g.

Here the pancreas remnant was slightly less than one-tenth of the whole. This record again shows that the diabetic process

is slow in getting under way; *i.e.*, the true diabetic glycosuria did not begin till January 2.

Date.	Urine, cubic centimeters.	Sugar, per cent.
Dec. 30	180	Faint
Dec. 31	No urination	....
Jan. 1	235	0
Jan. 2	260	5
Jan. 3	1855	2.9
Jan. 4	400	6.5
Jan. 5	Specimen	Heavy
Jan. 6	530	2.6
Jan. 7	405	5

Glycosuria continued till dog was chloroformed for autopsy on April 23.

Dog 184; male; age 2 years; weight 11,450 g.
[See protocol in Appendix.]

January 8, removal of pancreatic tissue weighing 22.6 g. Remnant communicating with main duct estimated at 3 g.

Here the remnant was a trifle less than one-eighth of the whole gland. The result was permanent diabetes gravis.

Dog 155; male; age 2 years; weight 12,550 g.
[See protocol in Appendix.]

November 24, removal of pancreatic tissue weighing 17.7 g. Remnant communicating with main duct estimated at 3.5 g. maximum.

Glycosuria remained absent till milk was fed on November 27, but then took the form of permanent diabetes gravis. The estimate, according to which the remnant amounted to nearly one-sixth of the pancreas, was probably high, but nevertheless diabetes here occurred with an exceptionally large remnant.

Dog 104; male; age 3 years; weight 10,465 g.
[See protocol in Appendix.]

October 1, removal of pancreatic tissue weighing 21.2 g. Remnant communicating with ducts estimated at one-fourth of the gland. No diabetes resulted, though the feeding experiments of October 21–24 showed that alimentary glycosuria (e saccharo) was easily produced.

On November 27, pancreatic tissue was removed to the amount of 6 g., leaving two considerable remnants, one about each duct. After the usual latent period, the feeding of milk on November 30 brought out glycosuria of 12 per cent, and permanent diabetes gravis followed. At autopsy on December 23, the total weight of pancreas-tissue found in the abdomen was 8.1 g. This is an example of the marked hypertrophy which sometimes occurs after partial removal of the pancreas.

2. Transient Diabetes Gravis.

Dog 25; female; age 2 years; weight 3665 g.

December 29, removal of pancreatic tissue weighing 8 g. Remnant communicating with both ducts estimated at 1.25 g. ($\frac{1}{7}$–$\frac{1}{8}$). Glycosuria on meat diet disappeared January 2, but could thereafter be produced by bread feeding.

Dog 148; male; age 1 year; weight 14,500 g.

November 16, removal of pancreatic tissue weighing 26.7 g. Remnant communicating with main duct estimated at 3.3 g.

Here the remnant was almost exactly one-ninth of the gland. Particular care was taken to avoid any trauma that might conduce to diabetes, though such a factor probably plays little or no part. There was the usual late onset of diabetes gravis (on November 19). A week after operation, the glycosuria came to an end.

After some experience, a transient case is generally recognizable by the failure of the glycosuria to increase. When it begins to diminish, one may be sure that it will disappear if meat diet continues. Carbohydrate food always brings it back, as did the feeding of milk in this case, on November 26.

The polyuria, independent of glycosuria, is worth noting here (daily urine between 1 and 2 litres, sugar-free).

Dog 176; male; age $1\frac{1}{2}$ years; weight 7950 g.

December 28, removal of pancreatic tissue weighing 23.6 g. Remnant communicating with main duct estimated at 3.2 g. ($\frac{1}{8}$–$\frac{1}{9}$).

December 29, no urination.

December 30, specimen, sugar-free.

Later, 20 cc., faint sugar.

December 31, 115 cc., faint sugar. Fed milk.

January 1, 310 cc., heavy sugar. 75 cc., faint sugar. Fed 500 g. meat.

January 2, 230 cc., 3.7 per cent sugar. Ate 790 g. meat.

January 3, 325 cc., 6 per cent sugar. Ate 220 g. meat.

January 4, 325 cc., faint sugar. 45 cc., doubtful sugar. Fed bread-and-meat.

January 5, 250 cc., heavy sugar. Fed bread-and-meat.

January 6, 425 cc., heavy sugar. Fed bread-and-meat.

January 7, 270 cc., heavy sugar. Fed bread-and-meat.

January 8, 430 cc., 18.2 per cent sugar. Fed bread-and-meat.

January 9, 485 cc., 10.4 per cent sugar. Ate 600 g. meat.

January 10, 310 cc., 4.8 per cent sugar. Ate 700 g. meat.

January 11, 280 cc., faint sugar. Removal of 0.56 g. additional pancreatic tissue. 65 cc., 1.7 per cent sugar.

January 12, 45 cc., 1.2 per cent sugar.

January 13, 95 cc., faint sugar.

January 14, 40 cc., no sugar.

January 15, 25 cc., no sugar. Ate 500 g. meat.

January 16, 180 cc., no sugar. Ate 575 g. meat.

January 17, 215 cc., no sugar. Removal of 0.6 g. additional pancreatic tissue.

January 18, 150 cc., no sugar.

January 19, 105 cc., no sugar. Ate 400 g. meat.

January 20, 225 cc., 4 per cent sugar. Ate 800 g. meat.

January 21, 375 cc., 7.3 per cent sugar. Ate 400 g. meat.

January 22, 455 cc., 6.46 per cent sugar.

Summary for Dog 176.

Here the remnant was slightly less than one-eighth of the gland. Food was necessary to bring out the glycosuria plainly. The urine of January 4 proved that the condition was to be transient. Carbohydrate feeding as usual brought out a heavy glycosuria, even as high as 18.2 per cent on January 8. Return to meat diet on January 9 and 10 proved that diabetes gravis was on the point of disappearing.

A trifle more pancreas-tissue was removed on January 11. Though normal dogs did not show glycosuria from operations about the pancreas, this dog on the verge of diabetes gravis did show it. But the glycosuria quickly ceased.

On January 17, another trifle of tissue was removed from the pancreas remnant. This time, the course of events was that proper for true diabetes gravis. No glycosuria whatever resulted till after the dog was fed on January 19. Then began the heavy characteristic glycosuria.

Operators wishing to produce diabetes may follow the motto, "If at first you don't succeed, try, try again." Removal of very little tissue sometimes brings on the disease in a predisposed dog. If proper use has been made of the omentum, the secondary operation is very easy and brief, and is borne with correspondingly little shock.

Dog 185; female; age 3 years; weight 9600 g.

January 9, removal of pancreatic tissue weighing 16.9 g. Remnant communicating with main duct estimated at 2 g. This operation, leaving about one-ninth of the gland in position, was followed by diabetes gravis lasting about a week.

Removal of 0.7 g. more tissue on January 17 caused no glycosuria, until bread was fed on January 20. Then it continued on meat diet; but the small excretion, and the rapid gain in weight of the dog, proved that it would not be permanent. The dog was sacrificed before the glycosuria disappeared, in order to obtain an autopsy at this stage.

3. Diabetes Levis.

Dog 38; female; age 2 years; weight 5370 g.

August 2, removal of pancreatic tissue weighing 13.7 g. Remnant communicating with main duct estimated at 2 g. The result of this operation, which left a remnant of between $\frac{1}{7}$ and $\frac{1}{8}$ of the pancreas, was diabetes levis. As usual, the glycosuria on bread diet was high.

August 22, on meat diet, the dog was able to assimilate perfectly a subcutaneous injection of 3 g. dextrose per kilo. This and the other injection experiments were discussed in Chapter VI.

The glycosuria that followed bread-feeding on August 17 was accompanied by polyuria. Also, beginning August 24, bread-diet caused not only glycosuria but also increase of urine. The sugar evidently acts as a diuretic.

On September 14, half a gram of pancreas-tissue was removed. There was no post-operative glycosuria. But the result of removing this small portion of tissue was the transformation of diabetes levis into permanent diabetes gravis.

Starvation beginning October 2 showed that the case was not very severe, for glycosuria disappeared within two days.

Dog 48; female; age 1 year; weight 8850 g.

July 5, removal of pancreatic tissue weighing 15.2 g. Remnant communicating with main duct estimated at 4 g. ($\frac{1}{4}$–$\frac{1}{5}$). On bread diet, the urine at first showed sugar three times, the highest percentage being 0.42 per cent. There was no further glycosuria.

Dog 74; male; adult; weight 6670 g.

August 19, removal of pancreatic tissue weighing 11.5 g. Remnant communicating with main duct estimated at 2.3 g.

Here the remnant was exactly one-sixth of the pancreas. The result of the operation was diabetes levis.

One phenomenon deserves special notice, for it is rather frequently met with. After a period of meat-diet without glycosuria, the dog was placed on bread-mixture on September 7. No glycosuria resulted till September 10; thereafter it was heavy. Some dogs with diabetes levis (like Dog 38) show glycosuria within a few hours after receiving starchy food. Others (probably milder cases), like the present dog, excrete sugar only after one, two, or three days of starchy diet. Deficient digestion or absorption is ruled out by the dog's rapid gain in weight. The explanation presumably is that the animals on meat diet have accumulated a considerable store of amboceptor. Carbohydrate diet imposes a heavier burden than the pancreas is able to carry, but the reserves in the tissues are drawn upon, so there is no glycosuria. But after one or more days these reserves are exhausted; there is no amboceptor except the insufficient amount which the pancreas can furnish, and therefore glycosuria appears.

Dog 80; female; age 7 months; weight 4430 g.

September 1, removal of pancreatic tissue weighing 7.9 g. Remnant, mostly about the two ducts, estimated at 1 g.

Here the remnant was a trifle more than one-eighth of the pancreas. The result of the operation was diabetes levis.

Dog 86; female; age 1½ years; weight 6890 g.

September 8, removal of pancreatic tissue weighing 13.75 g. Remnant communicating with main duct estimated at 1.6–1.7 g.

Here the operation left slightly less than one-ninth of the pancreas. After several days, transient diabetes gravis developed, which, passing away, left the usual permanent diabetes levis. The urine remained negative on meat diet till September 25. Then, feeding bread-and-meat mixture resulted in immediate heavy glycosuria. When milk containing glucose was fed, the glycosuria was further increased.

At autopsy, there was found the hypertrophy of the pancreas remnant which is frequent in these dogs; *i.e.*, the remnant weighed 3.8 g.

Dog 129; female; age 11 months; weight 8100 g.

October 31, removal of pancreatic tissue weighing 16.5 g. Remnant communicating with main duct estimated at 2 g. (less than $\frac{1}{9}$). Diabetes levis. Killed on account of distemper November 11. Pancreas-remnant weighed 4.85 g.

Dog 151; male; age 4 years; weight 12,700 g.

November 21, removal of pancreatic tissue weighing 31.6 g. Remnant communicating with main duct estimated at 3.2 g.

Here the remnant was less than one-tenth of the pancreas. Nevertheless the resulting condition was merely diabetes levis. The reason is apparently given by the autopsy, which was obtained fresh on December 4. The remnant then appeared as composed of absolutely normal pancreas-tissue, unchanged either to sight or to touch. The weight of the remnant was 11.3 g. The hypertrophy therefore was of unusual degree.

Dog 152; male; age 2 years; weight 13,360 g.

November 24, removal of pancreatic tissue weighing 27.7 g. Remnant communicating with main duct estimated at 4.4 g.

Here the remnant was between one-seventh and one-eighth of the pancreas. This is one of the rare cases in which there has been postoperative glycosuria in my series. It was not diabetes, because it appeared and disappeared too quickly, and because the dog two days later could take 250 cc. milk with only a trace of glycosuria. The later condition was diabetes levis.

The autopsy in this dog (killed December 5) showed a normal-looking pancreas-remnant weighing 10.4 g. — another example of unusual hypertrophy.

Dog 125; male; age 1 year; weight 11,300 g.

October 26, removal of pancreatic tissue weighing 22.4 g. Remnant communicating with main duct, perhaps also communicating with lesser duct, estimated at 2.4 g. ($\frac{1}{10}$—$\frac{1}{11}$).

The dog quickly developed distemper and ate almost nothing. Glycosuria occurred only on carbohydrate diet. Death November 8; pancreas-remnant weighed 7.7 g. — again a marked hypertrophy.

4. Miscellaneous Experiments.

These observations may be arranged in two groups:

A. Size of remnant preventing diabetes.
B. Influence of infection or weakness.

A. Size of Remnant Preventing Diabetes.

Dog 17; female; age 2 years; weight 9110 g.

March 9, removal of pancreatic tissue weighing 18.9 g. Remnant communicating with both ducts estimated at 4 g.

Here, with a remnant of $\frac{1}{5}$—$\frac{1}{6}$ of the pancreas, there was no glycosuria even on bread feeding, though the sugar-tolerance was lowered.

Dog 31; female; age 10 months; weight 2400 g.

Removal of pancreatic tissue weighing 7 g. Remnant communicating with both ducts estimated at 2 g. ($\frac{1}{4}$—$\frac{1}{5}$). No diabetes.

Dog 67B; male; age 2 years; weight 10,950 g.

Removal of processus uncinatus and processus lienalis pancreatis, weighing 13.5 g. Body of gland, left communicating with ducts, estimated at the same weight. No diabetes.

The dog died of extraneous causes, so that the sugar-tolerance was not tested. By the accurate subcutaneous method, a lowering of the tolerance in such an animal will probably be demonstrable.

Dog 87; male; age 1 year; weight 7900 g.

September 11, removal of pancreatic tissue weighing 14 g. Remnant communicating with main duct estimated at 2.5 g.

Here the remnant was $\frac{1}{6}$—$\frac{1}{7}$ of the pancreas. The dog was able to live on bread without glycosuria.

Dog 93; male; adult; weight 8400 g.

September 21, removal of pancreatic tissue weighing 21.2 g. Remnant communicating with lesser duct estimated at 2.6 g., and small shreds along the vessels.

Here the main remnant was one-ninth of the pancreas. At autopsy it weighed 3.3 g., which represents no unusual hypertrophy. Yet not even diabetes levis was present. The case is very exceptional, and it is possible that the fragments left along the vessels had an influence in preventing diabetes.

Dog 96; female; age 11 months; weight 8825 g.

September 26, removal of pancreatic tissue weighing 16.2 g. Remnant communicating with lesser duct estimated at 2.2 g.

Here the remnant was about one-eighth of the pancreas. Glycosuria was absent on bread diet, but alimentary glycosuria was easy to produce, as was proved when glucose was added to the feed on several occasions.

Dog 123; male; age 1 year; weight 11,100 g.

Removal of about three-fourths of pancreas; the remnant communicating with both ducts. No glycosuria after eating meat, bread, or milk.

Dog 140; female; age 4 years; weight 16,300 g.

Removal of pancreatic tissue weighing 27.2 g. Remnant communicating with both ducts estimated at 7.4 g. ($\frac{1}{4}$–$\frac{1}{5}$). No diabetes.

Conclusion.

With rare exceptions, remnants representing $\frac{1}{6}$–$\frac{1}{7}$ of the pancreas suffice to prevent diabetes.

B. Influence of Infection or Weakness.

Dog 33; female; adult; weight 5635 g.

Removal of pancreatic tissue weighing 10 g. One remnant left about each of the two ducts; combined weight of the two estimated at 2.5 g. ($\frac{1}{5}$). Death 3 days after operation from peritonitis. No glycosuria.

Dog 55; male; age 7 months; weight 5920 g.

Removal of pancreatic tissue weighing 13.4 g. Two remnants left, a larger about lesser duct and a smaller about main duct. Combined weight estimated at 1.6 g. (about $\frac{1}{9}$). Slight glycosuria for 3 days; then onset of severe distemper, and cessation of glycosuria.

Dog 57; female; age 9 or 10 months; weight 5800 g.

September 6, after starvation since August 31, removal of pancreatic tissue weighing 20.2 g. Remnant communicating with lesser duct estimated at 1 g.; remnant about main duct estimated at 0.25 g.

Death three days after operation. Weakness was the presumable cause of the absence of glycosuria.

Dog 61; female; age 2 years; weight 10 kilos.

June 9, removal of pancreatic tissue weighing 25 g. Remnant communicating with main duct estimated at 2.7 g. ($\frac{1}{10}$). Death from peritonitis ten days after operation. No glycosuria.

Dog 70; male; adult; weight 20 kilos.

August 2, removal of pancreatic tissue weighing 21 g. End of processus uncinatus, estimated at 2 g., left communicating with bowel through the duct, which was dissected out and preserved.

Death two days after operation from peritonitis. No glycosuria.

The purpose of the experiment was to determine whether the processus uncinatus has any different anti-diabetic activity than other portions of the pancreas. A similar procedure might be possible with the splenic end of the gland. The attempt, while perhaps feasible, was not repeated.

Dog 75; female; age 2 years; weight 9520 g.

August 22, removal of pancreatic tissue weighing 15.7 g. Remnant communicating with main duct estimated at 1.8 g. (about $\frac{1}{10}$). Intense diabetes, with glycosuria up to 9.1 per cent. Death five days after operation from peritonitis. The experiment is useful as showing that even peritonitis of acute course does not necessarily prevent heavy glycosuria.

Dog 76; female; old; weight 11,250 g.

Removal of pancreatic tissue weighing 21 g. Remnant communicating with main duct estimated at 3.4 g. ($\frac{1}{7}$–$\frac{1}{8}$). Death two days after operation from perforation of duodenum. Glycosuria 4.3 per cent.

Dog 77; male; age 2 years; weight 10,880 g.

Removal of pancreatic tissue weighing 18 g. Remnant about ducts estimated at one-third of gland. Death next day from pneumonia and shock. No glycosuria.

Dog 78; male; adult; weight 11,660 g.

Removal of pancreatic tissue weighing 15 g. Remnant communicating with main duct estimated at 2 g. ($\frac{1}{7}$–$\frac{1}{8}$). Death two days later from peritonitis. No glycosuria.

Dog 83; female; weight 7300 g.

Removal of pancreatic tissue weighing 26.3 g. Remnant communicating with main duct estimated at 3.1 g. ($\frac{1}{9}$–$\frac{1}{10}$). Death two days later from pneumonia. No glycosuria.

Dog 94; male; weight 9630 g.

Removal of pancreatic tissue weighing 16.65 g. Remnant communicating with lesser duct estimated at 2.3 g. (about $\frac{1}{8}$). Death three days later from peritonitis. No glycosuria.

Dog 103; female; age 3 years; weight 4225 g.

Removal of pancreatic tissue weighing 15.4 g. Remnant communicating with lesser duct estimated at 1.4 g. ($\frac{1}{12}$). No glycosuria. Death five days after operation; autopsy showed a small circumscribed abscess between pancreas and duodenum.

Dog 109; male; age 3 years; weight 14,900 g.

October 11, removal of duodenal end of pancreas, weighing 12.6 g. No glycosuria.

October 26, removal of 4.4 g. additional pancreatic tissue. Death three days later from peritonitis. Pancreas remnant at autopsy weighed 4.7 g. No glycosuria.

Dog 181; male; age 3 years; weight 17,800 g.

January 2, removal of pancreatic tissue weighing 20.8 g. Remnant communicating with main duct estimated at 2.25 g. (about $\frac{1}{10}$). Death two days after operation, from pneumonia. No glycosuria.

Dog 182; male; age 3 years; weight 14,520 g.

January 5, removal of pancreatic tissue weighing 19.6 g. Remnant communicating with main duct estimated at 1.6 g. ($\frac{1}{12}$). Death three days after operation from peritonitis. Glycosuria absent till day of death; then 2.9 per cent.

Dog 183; male; weight 7760 g.

January 5, removal of pancreatic tissue weighing 17.3 g. Remnant communicating with main duct estimated at 1.6 g. (about $\frac{1}{12}$). Death three days after operation, from localized peritoneal abscess not near pancreas. Glycosuria absent till day of death; then 1.9 per cent.

Conclusion.

Infection, either involving the general peritoneum or limited to the pancreatic region, is without specific influence upon the diabetes. Pflüger's supposition, that infectious irritation of the nerves about the pancreas may produce diabetes, finds no support; for glycosuria did not occur in cases of infection any more readily than without infection. On the other hand, infection has no specific influence in preventing glycosuria. Sometimes glycosuria seems to be prevented by the simple weakness associated with peritonitis, pneumonia, distemper, or shock. The behavior is irregular; for in other cases when the weakness is seemingly as great, glycosuria is not prevented. Several of these dogs show that intense glycosuria may coexist with intense peritonitis. The absence of specific influence is particularly well shown by Dogs 182 and 183. Here glycosuria was absent for two days after operation, and then it appeared, though the animals died shortly thereafter. The time-relations of its appearance were therefore similar to those seen in non-infected dogs.

5. Other Pancreatic Disturbances.

The literature furnishes evidence of the existence of other internal functions of the pancreas, besides the one concerned in

carbohydrate metabolism. This evidence may be summarized as follows.

1. "Total" diabetes from the carbohydrate standpoint may be present after incomplete pancreatectomy, without the other consequences of total pancreatectomy.

2. Suitable pancreatic operations may also produce polyuria and azoturia without glycosuria.

3. Fat-combustion (found by Falta to be accelerated in dogs after total extirpation) is presumably not thus accelerated in dogs with severe diabetes after partial extirpation.

4. Obesity may presumably sometimes represent a disease of the pancreas (clinically).

5. Absorption of food may be better after partial than after total pancreatectomy, even though the diabetes be severe in both cases.

6. Loss of resistance to infection, and of the hemolytic and bactericidal properties of the blood, follow complete but not incomplete extirpation. My dogs, with severest disturbances of sugar-utilization, could still withstand repeated peritoneal operations practically like normal dogs.

7. Infantilism may be a sequel of pancreatic disorder in the young. Opie (4) reviews the clinical literature of the subject as follows.

"Bramwell has described a case which he believes affords evidence that retarded development in children may be referable to pancreatic defect. A boy eighteen years old, who had suffered with diarrhea during nine years, had exhibited arrest of physical development after the eleventh year. Following the administration of glycerin extract of pancreas there was disappearance of diarrhea and rapid increase in weight. Thompson described two similar cases with diarrhea; a man of twenty-four had the appearance of a boy of ten and a boy of eighteen resembled a child of nine years. Improvement followed the use of pancreatic extract. Rentoul records a similar condition occurring in a girl with arrested development. Direct evidence of pancreatic disease in these cases is wanting, and there is some resemblance to the condition of infantilism from chronic intestinal infection described by Herter. Langdon-Brown saw a boy with congenital syphilis sixteen years of age who had the appearance of a child eight or ten years old; there was diarrhea with fatty stools. Pancreatitis believed to be syphilitic was found at autopsy."

Pratt (2) has reported infantilism resulting from atrophy of the pancreas, produced by ligation of the ducts, in one puppy. I am indebted to him for a personal communication concerning other observations of this nature, which he proposes to follow in further experiments. It is fully to be expected that pancreatic

atrophy will interfere with the proper growth and development of young animals. The study of pancreatic infantilism, and the possible influence of pancreas-feeding upon it, promises an interesting addition to our knowledge. The pancreas is presumably, like other glands of internal secretion, important for the normal growth of the body.

8. Cachexia may be a sequel of pancreatic operations, unrelated with glycosuria. After total pancreatectomy there is always intense and fatal cachexia, as well as the glycosuria. Sometimes after partial extirpation, there is glycosuria as intense as after the total operation, but cachexia is slight or absent. On the other hand, partial pancreatectomy, or ligation of the ducts, or especially the combination of the two procedures, may be followed by cachexia. Sometimes the cachexia is accompanied by glycosuria; sometimes there is no glycosuria, and even a considerable dextrose tolerance. The cachexia may be as rapidly fatal as typical diabetes. Again it may be a slow, gradual decline. The condition is to be sharply distinguished from the suppression of glycosuria by simple weakness; it is a totally different phenomenon. It presumably indicates disturbance of some specific internal pancreatic function, other than the carbohydrate function.

My observations on this point have been merely incidental, and may be grouped as follows:

A. Peculiar deaths.
B. Azoturia.
C. Cachexia with glycosuria.
D. Cachexia without glycosuria.
E. Cachexia in young animals.

A. Peculiar Deaths.

Several dogs, of which the records are omitted, have died from one to several days after partial pancreatectomy, when no explanation was furnished either by the clinical history or by the autopsy. In addition, mention may be made of the following three animals.

Dog 54 underwent Bernard puncture on May 16, lived thereafter in good condition, and reared a litter of pups. On October 5, most of the pancreas was removed. Death occurred the next day in a very peculiar state of collapse. The pancreas operation had been an unusually short and easy one, and no cause for the fatal condition was found.

Dogs 151 and 152, previously mentioned, were animals with diabetes levis, fat, lively, and apparently in full strength. Both died suddenly at the very outset of ether anæsthesia, and could not be revived.

Any or all of the above occurrences may be explained as simple coincidences. But it seems not improbable that the removal of the greater part of an important organ constitutes an injury in addition to the simple nervous shock, and that the animal is weakened in its vital powers.

B. Azoturia.

Dog 74 furnished a probable example. Most of the pancreas had been removed, and also Bernard puncture performed. During the period from November 18 to 23, the animal ate 500–800 g. meat daily, the feces were scanty and well digested in appearance, yet the body-weight fell from 6085 g. to 5560 g. There was no glycosuria, but the urine was abundant and of high specific gravity, 1052–1068. Analyses were prevented by extraneous circumstances; but the case gives the impression of "diabetes without glycosuria."

C. Cachexia with Glycosuria.

Dog 128; female; age 3 years; weight 5600 g.

October 29, removal of pancreatic tissue weighing 14.3 g. Remnant communicating with main duct estimated at 0.8 g. Diabetes gravis resulted as usual. Rapid downward course to death on November 5. Autopsy showed no cause. Glycosuria was up to 7.5 per cent.

Dog 149. November 16, removal of pancreatic tissue weighing 26.2 g. Remnant communicating with main duct estimated at 1.5 g. The heavy glycosuria, rapid decline, and death without discoverable cause on November 20 were mentioned previously in this chapter.

The above dogs are extreme examples, but it is a general fact that cachexia varies widely in different diabetic animals. It is not parallel with glycosuria. Neither does it depend upon the size of the pancreas-remnant, as is illustrated by Dog 19 (page 480), which had the smallest pancreas-remnant of the series, yet was a strong and long-lived diabetic animal.

D. Cachexia without Glycosuria.

Dog 95; female; old; weight 6500 g.

September 26, removal of pancreatic tissue weighing 16.1 g. Remnant communicating with lesser duct estimated at 1.45 g. (about $\frac{1}{12}$). The glycosuria which should have occurred under these conditions was entirely absent. Instead, there was polyuria and rapid loss of weight. The dog was killed on October 8, when it could have lived only a day or two longer. There were nervous symptoms on the last day.

Dog 106; male; age 2 years; weight 13,800 g.

October 6, removal of entire duodenal end of pancreas, weighing 11 g.

October 26, removal of splenic end, leaving remnant about lesser duct. No glycosuria. November 6, death after steady decline; no cause discoverable.

Dog 107; female; age $1\frac{1}{2}$ years; weight 8000 g.

October 10, removal of half of an unusually small pancreas (the half removed weighed only 4.9 g.). October 16, sutures removed; wound-edges separate with no sign of healing. The instance is mentioned in comparison with totally depancreatized dogs, whose wounds heal poorly.

Dog 111; male; age 3 years; weight 7050 g.

October 13, removal of pancreatic tissue weighing 16.7 g. Remnant communicating with lesser duct estimated at 1.8 g. The remnant was less than one-tenth of the pancreas, therefore diabetes gravis was to be expected, but it failed to appear. The weight fell to 5100 g., and on October 26 the dog was found dead, with no cause discoverable. Pancreas-remnant, healthy-looking, weighed 2 g.

Dog 121; female; age 11 months; weight 4120 g.

October 19, removal of pancreatic tissue weighing 13.2 g. Remnant communicating with main duct estimated at 1.1 g. Here the remnant was just one-thirteenth of the pancreas. The expected diabetes gravis did not appear. Death occurred October 27 without discoverable cause. Pancreas-remnant, healthy-looking, weighed 2.2 g.

Dog 126; female; age one year; weight 7660 g.

October 27, removal of pancreatic tissue weighing 15.8 g. Remnant communicating with main duct estimated at 1.5 g. Here the remnant was less than one-eleventh of the pancreas, yet diabetes gravis failed to appear. Instead, there was a rapid decline, leading to death on November 8. It is noteworthy that in these cases where the proportion of pancreatic tissue removed is such as ordinarily causes diabetes gravis, yet glycosuria fails to appear, the duration of life is generally far shorter than in cases where diabetes develops in typical form.

The above are examples of acute cachexia. A chronic case is the following.

Dog 24; female; age 2 years; weight $5\frac{1}{2}$ kilos.

December 27, removal of pancreatic tissue weighing 10.2 g. Remnant about lesser duct estimated at 1 g. Duct ligated. No glycosuria. Tests January 24–31 showed the dextrose tolerance to be low. There was a steady decline, and on February 23 the dog was chloroformed when near death. Pancreas remnant atrophic.

Conclusion. — Cachexia is the result of some pancreatic disturbance, independent of glycosuria. It is probably more frequent when the pancreatic ducts are ligated, but it may also occur when they are left free and when the pancreas-remnant appears normal.

E. Cachexia in Young Animals.

Pup 1B; male; age 3 months; weight 2110 g. Condition poor.

October 3, removal of pancreatic tissue weighing 7.5 g. Remnant communicating with lesser duct estimated at 0.8 g. ($\frac{1}{10}$–$\frac{1}{11}$). Death October 6; autopsy negative; no glycosuria.

Dog 27; female; age 7 months; weight 3430 g.

January 10, removal of pancreatic tissue weighing 7.75 g. Remnant communicating with lesser duct estimated at 1.5 g. Here the remnant was less than one-sixth of the pancreas; it was ample to prevent diabetes, yet after a slow cachexia, death occurred February 4.

Dog 30; female; age 9 months; weight 2700 g.

February 3, removal of pancreatic tissue weighing 9.5 g. Remnant communicating with both ducts estimated at 1 g. Post-operative glycosuria (one specimen); slow peritonitis; death February 10. Although the remnant was less than one-tenth of the pancreas, yet the pup could take milk without glycosuria.

Dog 55; male; age 7 months; weight 5920 g.

May 24, removal of pancreatic tissue weighing 13.4 g. Two remnants, one about each duct; combined weight estimated at 1.6 g. Here the tissue left was $\frac{1}{9}$–$\frac{1}{10}$ of the pancreas. Typical diabetes ensued, and the pup appeared well till acute distemper developed and caused death May 28.

Dog 62; female; age 4 months; weight 3700 g.

June 1, removal of pancreatic tissue weighing 14.25 g. Two remnants, combined weight estimated at 1.5 g. Here the tissue left was less than one-tenth of the pancreas; yet on June 4 a subcutaneous injection of 5 g. dextrose per kilo was nearly all assimilated and produced no diuresis. June 6, death. Autopsy shows one very small peritoneal abscess.

Dog 101; male; age 7 or 8 months; weight 5860 g.

September 30, removal of pancreatic tissue weighing 18.4 g. Remnant communicating with lesser duct estimated at 1.7 g. October 7, death from slow peritonitis. Remnant was only one-eleventh of pancreas; no glycosuria.

Dog 122; male; age 6 months; weight 3830 g.

October 20, removal of pancreatic tissue weighing 7.5 g. Remnant communicating with main duct estimated at 0.3–0.4 g. Remnant about lesser duct estimated at 0.6–0.7 g. (Total remnant = $\frac{1}{8}$–$\frac{1}{9}$.) Operation very short and easy; animal recovered consciousness and apparent strength very quickly. Death over-night, without discoverable cause.

Dog 134; female; age 8 months; weight 7200 g.

November 6, removal of pancreatic tissue weighing 18 g. Remnant communicating with lesser duct estimated at 1.8 g. ($\frac{1}{11}$). Very short easy operation; prompt recovery of strength; death over-night, without discoverable cause.

Conclusion. — The tendency to excessively severe glycosuria, as seen in the diabetes of children, is not found in puppies. While diabetes may probably be produced in young puppies, yet the tendency in them is for the pancreatic disturbance to be expressed by cachexia, frequently to the entire exclusion of glycosuria. The example of Dog 55 shows that in older puppies the course of diabetes may be typical.

Pancreas Operations in Species other than Dogs.

At the opening of this chapter, mention was made of the advantage of being able to experiment with diabetes in an animal, such as the dog, which is naturally subject to the disease. Not all species react alike to pancreatic operations; the differences correspond presumably to differences in their natural metabolic processes. The difference is not of such degree that the pancreas is a dispensable organ in any species; apparently in every animal possessing a pancreas, the total extirpation is a fatal procedure and is followed by diabetes. The diabetes does not always run the same course; *e.g.*, in selachians and in some birds there is hyperglycemia without glycosuria; but the diabetic condition is still recognizable. But by the method of partial extirpations, it is possible to distinguish more clearly the interesting differences in the reaction of different species. My experiments have extended only to cats and rats.

Cats. — These animals are entirely unsuited for diabetic experiments. After total pancreatectomy, although glycosuria is present, its intensity seems not to equal that in the dog, and acutely fatal cachexia and peritonitis predominate. Nearly total removals are likewise unsatisfactory; in one instance, I left only a few shreds, and the glycosuria was very slight; death occurred after ten days. For certain reasons, it appeared especially important to produce diabetes, if possible, in cats by the same method as in dogs, or to predispose them to diabetes by removal of considerable portions of the pancreas. Therefore I removed fractions of the pancreas, similar to those described in dogs, in ten cats, leaving the remnant communicating with the duct. The result in every case was rapid cachexia and death, without glycosuria, frequently with infection (though in other abdominal operations in cats, *e.g.*, upon the adrenals, there has been no such difficulty). Similarly Opie [(4), p. 185 ff] reports death in cats 20 and 25 days after ligation of the ducts. Dewitt found that

many cats died after duct-ligation, but a few survived. In the experience of Ssobolew (2), the cats either died or the ducts became reëstablished. Milne and Peters (1) were able to separate the processus lienalis from the rest of the pancreas (without removing tissue) in cats without fatal result. I was compelled to conclude that partial pancreas-extirpations, such as produce diabetes in dogs, are not feasible in cats; that cats are among the most sensitive of all animals to injury of the pancreas, but the pancreatic disorder is manifested by cachexia instead of glycosuria. If anybody can remove the greater portion of the pancreas in cats and succeed in making the animals live long enough, there is a very interesting field here in connection with emotional glycosuria and diabetes.

Rats. — Several partial extirpations in rats have been followed by no glycosuria. The most nearly complete operation was in one animal in which only small shreds were left, with doubtful duct-communication; nevertheless the animal thrived and showed nothing abnormal in appearance or digestion. On bread diet, the urine contained reducing sugar, as in normal rats; and the tests of the dextrose tolerance performed by the subcutaneous method in parallel with two normal rats showed very slight lowering of assimilation (about 4.5 g. per kilo as opposed to a little above 5 g. normal). The rat is known to be exceptional in its endurance of the loss of other glands of internal secretion, and it seems also exceptionally little affected by removal of most of the pancreas.

By the firm establishment of the fact that diabetes is easily and regularly produced in suitable animals by partial removal of the pancreas, provided that all unnecessary complicating factors are avoided, new possibilities are thrown open for the study of diabetes in different animal species. Some of these may be mentioned as follows.

Monkeys. — These animals are first and preëminent in importance in this connection. Much undue mystery has been thrown about the pancreas by the erroneous supposition that a tiny fraction of the organ can discharge the internal function of the whole. There is a vague general impression as though much of the pancreas-tissue were superfluous from the standpoint of metabolism. It has accordingly seemed a puzzle, that diabetes may occur clinically with so little alteration in the pancreas; and

doubt has thus been cast upon the pancreatic origin of human diabetes. In dogs, true diabetes occurs when $\frac{7}{8}$—$\frac{9}{10}$ of the pancreas is removed. There is reason for believing that man is more susceptible, and that diabetes will occur when there is anatomical or functional loss of less than this fraction of the gland. [*e.g.*, the case described by Opie (4), pp. 110–111, of diabetes in a human patient after removal of two-thirds of the pancreas, though there may be some question as to what part infection and other influences played.] The animal to furnish the best information on the subject is the monkey. It seems probable that diabetes may occur in monkeys when more than one-eighth of the pancreas is left in its normal position. If diabetes occurs in monkeys under these conditions, the human disease becomes more easily comprehensible; since it is evident that diabetes is possible in the presence of a considerable mass of normal pancreatic tissue. Furthermore, the monkey is the animal whose metabolism, including the tendency to acidosis, most nearly resembles that of man; and diabetic monkeys would appear to be the best objects for the study of disputed problems of this nature, for which the dog is in some ways poorly suited.

Pigs. — Minkowski [(1), p. 9] produced a satisfactory type of chronic diabetes by partial pancreatectomy in a pig. The pig is known to be in some respects a valuable laboratory animal. As an omnivorous animal, it may have some advantages over carnivorous animals for metabolic studies. It seems probable that by the method described for dogs, a very useful type of diabetes may be produced in pigs.

Rabbits and Guinea-Pigs. — These animals have been favorites for the study of duct-ligation, and it is well established that in them the acinar tissue may disappear and the islands of Langerhans alone persist, while diabetes remains absent. But true diabetes has never been produced in these animals by any method; and until their susceptibility to diabetes is established, the results of duct-ligation lack theoretical conclusiveness. The rabbit has a naturally high dextrose tolerance; other organs perform the digestion perfectly when the pancreas is lost; and it is fully conceivable that diabetes may be impossible to produce in it. The guinea-pig is an animal of low dextrose tolerance. There is good reason to hope that this tolerance will be greatly lowered by removal of suitable portions of the pancreas; and the prospect of diabetes is increased by the high carbohydrate content of the

animal's natural food. Furthermore the islands of Langerhans in the guinea-pig are particularly well developed and specialized, and have been the object of important histological studies. The diffuse distribution of the pancreatic tissue, which has discouraged attempts at total extirpation, does not necessarily preclude success by the method of partial extirpation as described in this chapter. The possibility of producing diabetes in rabbits and guinea-pigs should at least be worth trying.

Frogs. — The frog's sugar-tolerance is particularly low. If the tolerance is much reduced by removal of the greater portion of the pancreas, the animal must presumably become diabetic. Previous workers, attempting total extirpations, have inflicted extensive and fatal injuries. But if the extirpation is carefully performed, sparing the bile-duct and important veins, and leaving the small portion of pancreatic tissue in relation with these structures, there is some possibility that an interesting form of diabetes may result, with considerable duration of life. The onset would presumably be late.

Birds. — Only experiment can decide whether diabetes may result from partial pancreatectomy in the various avian species. There is an advantage in the possibility that, if a fragment of pancreas is left secreting into the bowel, the rapid cachexia may remain absent; digestion should certainly be improved. Experiments in this direction should offer theoretical interest.

General Conclusions.

1. The internal function of the pancreas is a very active and necessary function, and the substance which it furnishes is constantly and actively consumed in metabolism. When the organ is entirely removed, the supply of its internal secretion is exhausted within a very few hours. The normal pancreas is necessary for normal carbohydrate metabolism. Every important reduction of pancreatic tissue results in a demonstrable reduction of the dextrose tolerance. This reduction approaches more and more closely to the point of diabetes, till in the dog a mild diabetes results when approximately seven-eighths of the gland is removed, and a severe diabetes when approximately nine-tenths of the gland is removed. It is considered probable that man and the monkey may become diabetic more easily than the dog.

2. In addition to the internal function in relation to carbohydrate metabolism, the pancreas possesses other important internal functions.

3. The conclusions tentatively formed from dextrose injections in normal animals are here confirmed in diabetic animals. So far as observable in diabetic dogs, the complications of diabetes are not due to the sugar-content of the blood or urine. The following complications may be enumerated in this connection:

(*a*) *Wound-healing and Resistance to Infection.* — It is considered to be positively established that these complications are not due to hyperglycemia nor to disturbance of the carbohydrate function of the pancreas, but rather to disturbance of some other pancreatic function. Dogs after the most intense and prolonged glycosuria have withstood operations perfectly and their wounds have healed normally. They may also receive large subcutaneous sugar-injections without infection, and the same is true when the pancreas has been completely removed (Dog 65, Chapter VI).

(*b*) Albuminuria has not been found to result from the most intense and prolonged glycosuria. The previous conclusion (Chapter III) is thus confirmed, that the albuminuria and renal injury following large doses of sugar are due to the sudden osmotic disturbance, not to the percentage of sugar in blood or urine.

(*c*) Fatty or fibrous changes, in the aorta (Dogs 154, 161, 171) or in the smaller vessels found in examining the various tissues, were absent (Chapter XXI).

(*d*) The sexual glands and sex-cells have been found normal [Chapter XXI].

(*e*) Nervous disorders, skin diseases, cataract, etc., have been absent.

There are no symptoms whatever which can be attributed to the physical or chemical effects of the circulating sugar. A prolonged abnormal state of the blood, of this nature, is apparently tolerated or compensated.

CHAPTER XI.

DIABETES INSIPIDUS.

THIS disease or symptom-complex is defined by Futcher (2) as follows: "A chronic affection, characterized by the passage of large quantities of pale urine of low specific gravity, free from sugar, albumin, and casts, and usually accompanied by an insatiable thirst."

Clinical Literature. Theory.

The following clinical details are also taken from Futcher. The disease is rare, and commonest in the young. Classification is possible into an *idiopathic* form, without known cause or anatomical basis, and a *symptomatic* form, in which there is organic disease in the nervous system or elsewhere. Among the latter cases, the commonest etiologic agents are injury of the brain (rarely of the spinal cord), brain tumor, brain syphilis (gumma or meningitis), spinal disease, diseases of various viscera (such as carcinoma of liver, aneurism of carotid or aorta), and rarely an abdominal trauma. It has also been known to follow the simple infectious fevers. It may be hereditary. The patients are generally of nervous type. Fright has been known to be the exciting cause. It is not to be confused with hysterical polyuria. The onset is frequently sudden. Polyuria may be enormous, even to 43 litres per day. The specific gravity is generally 1001 to 1005. Appetite may be normal, or in other cases may equal the polyphagia of diabetes mellitus. Cataract has been described. Extreme weakness may precede the end. Death is ushered in by drowsiness followed by coma. The idiopathic form is generally the more benign, and has been known to last for 50 years. In the secondary or symptomatic cases, emaciation may be rapid and death come early.

Mohr, in von Noorden's "Metabolism and Practical Medicine," summarizes the known facts concerning the metabolism in diabetes insipidus. The energy exchange and protein metabolism are practically unaltered. Water economy is disturbed, in that the ingested water is more slowly excreted than by normal persons;

the condition is called bradyuria. The opposite change, tachyuria, a more rapid excretion than normal, has been described. Inosit may be found in the urine, but as it is not always present, and may occur in the urine of normal persons after excessive water-intake, its presence is without significance. Other constituents of the urine are generally normal, except for the dilution. Mohr accepts the essential inability of the kidneys to concentrate the urine as the cause of the disease.

Restriction of water was formerly a favorite therapeutic method in diabetes insipidus. In some patients, after a few days of thirst, the urine returns to normal and the desire for excessive drinking is lost. In a larger number of cases, thirst remains urgent and the patient's health suffers unless water is given. Present opinions classify the former type as primary polydipsia, the latter as primary polyuria or true diabetes insipidus. Some of the literature pertaining to the disease is as follows.

Futcher (3) reported five cases, and reviewed the subject up to 1902.

Heresco in 1903 reported one case of diabetes insipidus cured by nephropexy.

Tallqvist in 1903 described experiments upon a case of diabetes insipidus, proving that the concentration of the urine is very slightly affected by diet, but that the quantity varies with the amount of solid ingredients which must be excreted on a given diet. This test and the conceptions of the disease based upon it have since played an important part.

Strauss (1) in 1905 studied the water-economy, and agreed with Kraus (Ztschr. f. Heilk. 1887) that tachyuria rather than bradyuria is present. His observations support the view of primary polyuria as opposed to primary polydipsia.

Meyer in 1905 defined diabetes insipidus as a primary polyuria, resulting from inability of the kidney to concentrate urine. For this reason, the kidney reacts to changes in diet by changes in the quantity of urine, instead of the usual changes of concentration. Doses of NaCl serve to distinguish patients with true diabetes insipidus from cases of primary polydipsia. Theocin produces in diabetes insipidus an increase of concentration without increase of quantity. Sodium phosphate is excreted without increase of urine, just as in the normal subject.

In 1907, observations were published by Segallow, by Winkelmann, and by Finkelnburg. Seiler in the same year further con-

firmed the view that the disease consists in a loss of concentrating power by the kidney. In his hands, however, theocin merely caused polyuria, not the increased concentration reported by Meyer.

Engel (1 and 2) published two cases, one typical of primary polyuria or true diabetes insipidus, the other typical of primary polydipsia. The distinctions between the two are set forth. Engel surmises that in diabetes insipidus a prolonged nervous stimulus (probably from the medulla) excites the glomeruli to greater secretion or the tubules to diminished resorption, or both.

Ebstein in 1909 reviewed a series of cases reported by others, and added several of his own. He concludes that diabetes insipidus has its basis in the nervous system, and the nervous foundation is generally laid by trauma, syphilis, or the like. There are two essential symptoms, viz., polydipsia and polyuria; each may influence the other; both are manifestations of the nervous disorder; and there is no reason for insisting that polyuria must always be primary rather than polydipsia. All other symptoms are complications, or are referable to the particular nervous cause (as bulimia may be present in secondary syphilis). Not withdrawal of water but withdrawal of salt is the correct treatment.

Schwenkenbecher in 1909 published an etiologic study. He recognizes an acquired tolerance for water in diabetes insipidus, on the part of the kidneys and the entire body, and compares it to acquired tolerance for morphine, alcohol, etc.

Traumatic polyuria is discussed in a paper by Schümann in 1910.

Forschbach and Weber published important studies in 1911, seriously disputing the long-accepted views of Meyer. Their cases were proved to be primary polyuria by withdrawing water; on limited water-intake the excretion exceeded ingestion, with a corresponding loss of body-weight, thus proving a drying of the tissues by the abnormal urine-secretion. By feeding salt, and comparing the resulting urine not with the normal (as did Meyer), but with the patient's own urine before the dose, they conclude that the kidney often shows a very satisfactory concentrating power. This *relative* concentrating power is in their opinion the true test, and shows no departure from the normal. Here they agree with Finkelnburg. But sodium chloride is concluded to be a more active water-diuretic for the diabetes insipidus patient than for the normal; the kidney is supersensitive to salt. With-

drawal of salt does not always correspondingly diminish urine; also in Finkelnburg's cases, water excretion may precede salt-excretion; accordingly the water-excretion is to be looked upon as something more than a mere dilution of the salt. Fever may cause a diabetes insipidus patient to excrete urine of normal concentration. The authors found that the same can be accomplished by opium. They conclude that the kidney has not lost the power of concentrating salt in diabetes insipidus.

Relation with Organs of Internal Secretion.

The primary cause of diabetes insipidus is at present and with greatest probability being sought neither in the kidney nor in the nervous system, but in organs of internal secretion.

Stuber in 1911 studied a case of primary polyuria or true diabetes insipidus. As usual, on salt-free diet, meat diet, vegetable diet, etc., the concentration of the urine remained consistently low, thus proving the inability of the kidney to concentrate. Small doses of NaCl subcutaneously, or 30 g. NaCl by mouth, or even 2 g. calcium lactate, produced elevation of temperature, and repetition brought no "immunity." There was an increase of adrenalin in the blood as measured by the Trendelenburg method. Adrenalin "crises" are described, viz., periods of increased adrenalinemia; and increased diuresis accompanied such periods. Small doses of adrenalin slightly increased the diuresis. The author brings together the notions of Freund and others [see Chapter V] concerning parallelism between salt-fever and adrenalin-fever, and the alleged relation to the state of the sympathetic and the chromaffin system, and considers therefore that diabetes insipidus is a manifestation of adrenalinemia, an increased function of the chromaffin system.

Several authors, *e.g.*, Hewlett, have reported in connection with hypophyseal troubles a polyuria, resembling mild diabetes insipidus. The conception of diabetes insipidus as a disease of the hypophysis has recently been advanced by E. Frank. It is more probable than the chromaffin-tissue hypothesis, and notice may be taken that it explains Freund's observations very well; for Kepinow has recently demonstrated the synergism of hypophyseal extract and adrenalin, and the reactions observed by Freund could thus be explained by hypophyseal over-function.

E. Frank reviews much of the literature of this subject, especially as pertaining to the hypophysis. In particular, the experi-

mental findings of Schaefer and co-workers are emphasized, viz., that hypophyseal extract (pituitrin) is a powerful diuretic; also that mechanical or thermic injury of the exposed hypophysis may give rise to long-continued polyuria. The effects are attributed to the pars intermedia. Frank then analyzes a series of clinical cases, showing the frequent association of diabetes insipidus with hypophyseal lesions or symptoms (bitemporal hemianopsia, dystrophia adiposo-genitalis). Likewise the so-called "symptomatic" diabetes insipidus, the result of trauma, syphilis etc., is attributed to hypophyseal irritation. In the hereditary form, an inherited abnormality of the hypophysis is considered more probable than an inherited state of the nervous system, especially as obesity or other signs frequently accompany these conditions.

Herrick has described a patient aged 43, with polyuria of 4 years duration. The quantity was 7500–11,000 cc. daily, specific gravity 1001. By lumbar puncture, 5 cc. of fluid was obtained, dropping slowly under low pressure. Headache, vomiting, and general weakness followed; morphin was given for pain; the urine dropped to normal within 48 hours and remained so for 4 weeks. A later report indicates that the polyuria is slowly returning. The author makes the point that the kidney evidently retains the power of concentrating urine under some conditions. A cerebral, perhaps hypophyseal, etiology of diabetes insipidus is suggested.

Relations with Diabetes Mellitus.

Some authors have described relations between diabetes mellitus and diabetes insipidus, and alleged transitions of one into the other. Naunyn (p. 49) reviews a few cases in the literature, states that he has seen glycosuria only once with diabetes insipidus, that tests with ingestion of 100 g. dextrose have proved negative, and that he cannot support the belief of transition of diabetes insipidus into diabetes mellitus. Von Noorden [(1), p. 126] admits that frequently a considerable period of polyuria may precede the glycosuria in diabetes mellitus. The urine has low specific gravity and behaves as in diabetes insipidus. But it is better to speak of premonitory polyuria than of diabetes insipidus. "For true diabetes insipidus is a disease sui generis, and has nothing to do with diabetes mellitus." After disappearance of glycosuria in diabetes mellitus, there is often a period of polyuria. But this is due merely to continuance of the patient's habit of

drinking excessively; when water is restricted for a few days, the thirst and polyuria both disappear. Lepine [(1), p. 413] cites authors who have found diabetes insipidus and diabetes mellitus running in the same family. Lepine himself observed one such instance. He remarks that the observations of transitions between mellitus and insipidus are frequently not precise; but, in general, his position seems to be favorable to the belief in relations between the two diseases.

Heiberg (10) mentions Küster's report of polyuria with albuminuria following removal of a pancreatic cyst; and the collection by Gerhardt of this with a number of other reported instances, in which disturbance of the splanchnic nervous system is assumed as the cause of the polyuria.

Hoppe-Seyler described a case of continued polyuria and transient glycosuria, in which autopsy showed lipomatosis of the pancreas, with arterial changes and pigment-deposit in the interstitial tissue. He compared it to the polyuria that may follow partial extirpations of the pancreas.

Senator (1*A*) discussed this subject, and reported the case of a woman who from childhood had suffered from polydipsia and polyuria, passing 12–15 litres of urine per day, with a specific gravity of 1001–1003, without albumin or sugar. At the age of 40, sugar 0.3 per cent was found in her urine, and glycosuria was demonstrated repeatedly thereafter. She came under observation at the age of 43, having failed rapidly since the beginning of glycosuria. She died in extreme emaciation, and autopsy was negative.

Englemann (Diss. Göttingen, 1899) is quoted by Heiberg (10) as having collected several dozen cases, in which diabetes insipidus is supposed to have followed diabetes mellitus. It must be remembered that most such observations are rather carelessly made.

Blackett described a man aged 54, with diabetes insipidus secondary to psychic trouble, who died in coma, and sugar was found in the final urine.

Kuhn contrituted one of the best cases. The patient was a woman aged 58, with cancer of the breast and internal metastases. In 1899 there was an empyema operation. In April 1900, there was polydipsia and a polyuria up to 7 litres. From May 6 to 20 she had fever. All this time, sugar was constantly absent from the urine. On May 30, 1.8 per cent dextrose suddenly

appeared in the urine, while the quantity dropped to 4½ litres. Similar glycosuria continued till death, on May 28. The autopsy showed carcinomatous metastases in the lymph-glands about the cœliac plexus, and in one of the adrenals. The pancreas was atrophic.

Marano described a patient with polyuria since childhood. At the age of 17, he sustained a severe fall upon the occiput. At the age of 32, he noticed increased polyuria, general weakness, and failing vision. The urine was free from albumin, and contained 200 g. sugar in 24 hours.

D'Amato reported the case of a woman of 38, with greatly enlarged cervical lymph-glands. She gave a history of sudden onset of polyuria in childhood, and continuance of it throughout life. At the age of 34, while nursing her second child, she began to notice increased appetite, and loss of weight and strength. Her urine at the time of observation was 8 litres per day, and contained over 5 per cent sugar, without albumin or acetone. On strict diet the sugar diminished, but acetone appeared. She then passed from observation.

French and Ticehurst described the case of a man who sustained a fracture of the skull by a fall from a carriage. It was followed by double temporal hemianopsia and a polyuria of 10 litres without albuminuria or glycosuria. Attempts to demonstrate alimentary glycosuria gave negative results. Two years later, his physician discovered sugar in his urine. Examination in hospital then showed that his daily excretion was over 100 g. On strict diet this quantity diminished to 15 g.

Mann reported a patient with polyuria followed by glycosuria. Autopsy showed a cancer of the lesser curvature of the stomach, adherent to the pancreas.

Carter described a case of acute diabetes insipidus with fatal coma. There was no glycosuria, nor was acidosis present.

Brayton reported three cases of diabetes insipidus without glycosuria, in which not only the dryness of the skin but also itching was present, as in true diabetes.

Teschemacher (1) discussed the continuance of polyuria after cessation of glycosuria in diabetes mellitus, and transitions of mellitus into insipidus. The former is rather frequent, and may in his opinion be of central origin. Three cases of supposed transition are reported. One of these concerned an infantile brain-trouble, followed by a diabetes which alternated between mellitus

and insipidus; that is, in the course of a number of years, two such transitions occurred.

Heiberg (10) reported a patient aged 39, with polyuria from childhood. Since 1894 he had complained of stomach trouble. In 1906 his life was insured at the ordinary rate; but in 1907 sugar was found in his urine. Glycosuria ceased on strict diet, but the diuresis was 4–5 litres daily. Death occurred in coma. Autopsy showed the tail of the pancreas completely replaced by connective tissue, and the body of the gland transformed into a lipoma, containing very little pancreatic tissue. The few acini showed considerable atrophic change; the islets present were mostly normal.

Experimental Literature.

Aside from the above-mentioned hypophyseal experiments of Schaefer, the experimental production of conditions resembling diabetes insipidus may be reviewed as follows.

It is well known that Claude Bernard found a point in the floor of the medulla, just in front of the "glycosuric centre," where puncture frequently produces polyuria without glycosuria, but sometimes with albuminuria. Such polyuria is transient, seldom continuing more than a few hours. Later tests have shown that the power of concentrating urine is not lost. The condition is therefore not a true reproduction of diabetes insipidus, just as the typical piqûre does not give a true reproduction of diabetes mellitus.

Eckhard found that cutting the splanchnic nerves in dogs causes an increase of urine to four times the normal. Stimulation of the peripheral end of the cut splanchnic stops the polyuria. The vagi have no effect upon the urine output. Section of the spinal cord at the sixth or seventh vertebra caused suppression of urine. The fibres governing the renal function were found to pass from the medulla into the cord, and to leave it by the upper thoracic nerves, about the level of the sixth or seventh cervical vertebra. They follow the splanchnics, then the aorta and the renal arteries to the kidneys. In rabbits, polyuria often resulted from injury of the vermiform process of the middle lobe of the cerebellum, and also of points in the floor of the fourth ventricle other than Bernard's "centre." Results were especially marked after injury of the most posterior of the convolutions of the middle lobe of the cerebellum, as seen from above. He gave this the

name of "lobus hydruricus et diabeticus," because of the polyuria following its injury, and because the urine sometimes also contained sugar. Deep injuries of the brain in the temporal region were also sometimes followed by polyuria.

Kahler reported the production of persistent nervous polyuria. His method was to drill through the skull in rabbits, and then with a syringe inject a few drops of strong silver nitrate solution. Such an injury of the middle lobe of the cerebellum caused polyuria which generally ceased after a longer or shorter period, whereas after injection into the medulla the polyuria was permanent. The most suitable areas were the trapezoid body of the pons, and the lateral part of the uncovered portion of the medulla. In this region of the human brain the sixth and seventh cranial nerves take their exit, and analogy was thus found for the paralysis of the sixth nerve sometimes seen in diabetes insipidus. Also, destruction of the inner part of the cerebellum with Dieter's nucleus and its caudal processes almost always caused permanent polyuria.

Finkelnburg tried to imitate Kahler's methods, but was able to obtain polyuria for only a few days. This polyuria begins promptly after the operation, and amounts to 4 or 5 times the normal output. The polyuria in these cases is primary, and diuresis is secondary, yet tests show that the kidney has not lost its power of concentration. Finkelnburg used this fact as an argument against the idea of loss of the concentrating power in diabetes insipidus.

A different line of research which has frequently given rise to experimental polyuria has consisted in partial extirpations of the pancreas. Such polyuria without glycosuria was witnessed by Thiroloix (5), and by numerous later operators. Apparently, however, a permanent polyuria, or anything resembling true diabetes insipidus, has never been produced. The polyuria after such operations has always passed on into glycosuria, or else ceased.

A line of research apparently foreign to the subject will now be briefly introduced.

Claude Bernard (3) devised a method of obliterating the portal vein in dogs, by tying a stout ligature loosely about it and allowing the ends to protrude outside the abdomen. After a certain time, the ligature ulcerated out, proving the vein to be obliterated. Glycosuria occurred on starchy diet in such dogs, and was inter-

preted by Bernard in accordance with his views of the hepatic function. There is no statement concerning the diuresis. This subject must be considered at greater length in Chapter XX.

The Eck fistula has replaced Bernard's obliterative method, which is now practically forgotten. De Filippi (1), working with Eck fistulas, remarks that the dogs generally show slight oliguria, but one of his series exhibited marked polyuria. But he could not prove that the polyuria had not existed spontaneously before operation, therefore he mentioned the case only as an exception.

Burdjenko in 1909 published a method of obliterating the portal vein, different from Bernard's. There seems to have been no special notice of diuresis.

Gilbert and Lereboullet (1, 2, 4, and other publications) have made extended observations concerning the "rhythm" of the urinary output of water and solids in various conditions. In (4), they describe the phenomenon of *opsiuria*.

Lecerf, under Gilbert, devoted a thesis to opsiuria. It is defined as a retardation of elimination of water after meals. The patient undergoing the test should receive only two meals per day (*e.g.*, at 12 and 8 p.m.), and drink nothing between. The urine is collected in 4-hour specimens. The normal person shows digestive polyuria and fasting oliguria; the opsiuric patient exhibits digestive oliguria and fasting polyuria. Opsiuria is present in many liver diseases, including cirrhoses and passive congestions, with or without ascites. Diseases of the heart, kidneys, and organs other than the liver, are not accompanied by opsiuria. The sign is supposed to depend upon delayed absorption of fluid from the intestine on account of increased portal blood-pressure. It is an early indication of such tension in the portal system.

Gilbert and Villaret were able by partial ligatures of the portal or mesenteric veins to produce opsiuria and oliguria in dogs.

Opsiuria as a clinical test seems not to have gained general adoption, but is of interest as showing the delayed and diminished secretion of urine (consequent on slow absorption), which is caused by increase of pressure in the portal vein.

Gilbert and Chabrol (1) reported the effects upon the pancreas produced by partial ligatures of the portal vein or its tributaries. The ease with which such effects can be produced is attributed to the richness and fragility of the pancreatic capillaries. Examination 2–10 months after operation showed various stages of chronic pancreatitis. Congested veins and capillaries were prominent.

Degenerative changes were present in both acini and islets, with invasion of fibrous and fatty tissue. The authors' conclusion is that it is possible to produce sclerosis of the pancreas by portal ligatures.

Natus (1) studied exhaustively the effects of stasis upon the pancreas. His long paper cannot be summarized here further than to say that the changes are those of chronic inflammation. The studies were made in connection with a theory of chronic inflammation.

Experiments.

Without attempting to bring the scattered literature into order, I shall pass to the records of my experiments. All of them were merely incidental in the course of the study of diabetes mellitus.

Dog 32.

February 14, removal of pancreatic tissue weighing 12.4 g. Remnant about small duct estimated at 1.8 g. The duct was evidently a supernumerary one, for at autopsy only a pin-head nodule of pancreatic tissue was found secreting into the bowel, while the rest of the remnant was extremely atrophic.

For several days after operation there was marked increase of thirst and of urine, and thereafter the urine tended to be copious and pale (500–765 cc. per day, sp. gr. 1020–1040). There was no glycosuria, and the carbohydrate tolerance was considerable. But in the subsequent metabolism experiments, it was observed that ingestion of water was followed by a rush of almost water-pale urine, after which the urine became abnormally scanty and decidedly heavy. The later observations were made when the dog was receiving water regularly by stomach tube, 200 cc. at 9:30 a.m. and 200 cc. at 5 p.m. every day. The one daily meal was given in the evening and eaten promptly. Reference to Chapter VI (p. 345) will show that on April 6 the urine secreted from 9:30 a.m. to 1 p.m. was 180 cc., from 1 to 5 p.m. was 10 cc. On April 12 the 9:30–1 p.m. urine was 220 cc., the 1–5 p.m. urine 8 cc. On April 15 the 9:30–1 p.m. urine was 300 cc., the 1–5 p.m. urine 6 cc. These observations were possible when the diuresis was not modified by sugar-injections on the same or preceding days. During periods not recorded in detail in the record, the same general behavior was noticeable. Other dogs with similar pancreatic conditions have not been thus studied. But the curve of diuresis in

this animal was entirely different from that shown by my normal dogs, or by the numerous animals with partial pancreatectomy without closure of the ducts. Investigators working with dogs with pancreatic atrophy might perhaps take note, when convenient, of the curve of diuresis.

Dog 97 (weight 12 kilos).

On September 27, pancreatic tissue weighing 26.9 g. was removed, leaving a remnant estimated at 2.6 g. about the lesser duct. Autopsy on December 1 showed that the duct had been closed, leaving only a tiny nodule of pancreas secreting into the bowel, while the greater part of the remnant atrophied. After operation, the urine gradually increased. The animal was not catheterized, and was allowed on the roof during a considerable part of each day for exercise. A maximum was always retained and voided as soon as the animal reached the roof. Yet notwithstanding these conditions, the quantity passed in the cage was often near or above a litre, always pale and light. On October 22, a specimen obtained by keeping the dog confined for 24 hours was 1475 cc., specific gravity 1020; a similar specimen on October 28 was 1190 cc.; in such cases, allowance must still be made for a quantity retained in the bladder. Glycosuria was absent on bread diet except when a considerable quantity of commercial glucose was mixed with the feed; glycosuria was then very heavy, and the polyuria slightly increased, perhaps because of salts contained in the impure glucose. The general health, strength, and behavior were excellent. The following points may be noted.

The appetite was very large, but only on account of poor digestion. It does not explain the polyuria, for there was a large loss of water in the soft or liquid feces. The thirst was enormous.

On October 28, the diet was changed from bread-and-meat mixture to meat only. The polyuria still continued, and the specific gravity, as nearly as could be judged by partial specimens, was not altered. The kidney evidently retained a concentrating power; for certain specimens (probably secreted during fasting) showed much higher specific gravity than the others.

On October 30, large amounts of fresh pancreas were fed in addition to the meat. The impression was given (by partial specimens) of an increase of the specific gravity of the urine during the period of pancreas-feeding (to November 5).

On November 6, by laparotomy, the pancreas and its neighborhood were freed from adhesions. There was no effect upon the polyuria.

On November 14, a Bernard puncture was performed. The polyuria immediately ceased and remained absent, while the specific gravity correspondingly rose. On November 24, the piqûre was repeated, without further influence upon the diuresis.

Dog 148 (weight 14,500 g.).

On November 16, pancreatic tissue weighing 26.7 g. was removed, leaving a remnant estimated at 3.3 g., communicating with main duct. Diabetes gravis existed for some days following the operation; its cessation was perhaps due to hypertrophy of the pancreas remnant, which at autopsy was found to weigh 13.3 g. Marked polyuria persisted permanently (over a litre per day). Azoturia was perhaps present, for the specific gravity of the urine was not specially low, and the dog's appetite was very large. The general health was excellent. On December 11, Bernard puncture was performed, and stopped the polyuria permanently. Puncture was repeated on December 15. Normal diuresis continued till death, and autopsy showed the punctures well placed.

Dog 154 [see protocol in Appendix].

On November 24, pancreatic tissue weighing 23 g. was removed, and a remnant estimated at 5 g. was left communicating with main duct. There was no diabetes, but the urine increased to over a litre per day. The animal was close on the verge of diabetes gravis, as proved by the glycosuria caused by heavy meat-feeding December 2–5. [This dog and Dog 38 are the only ones in my series in which an increase in the quantity of meat produced glycosuria.] On December 7, extensive dissection and trauma about the pancreas remnant diminished the urine temporarily, but by December 13 the polyuria had returned. On December 15, Bernard puncture was performed. Glycosuria above 2 per cent resulted, but the immediate oliguria was striking. There was no return of polyuria. On December 22 the dog was made diabetic by removal of a trifle more of pancreatic tissue, and the subsequent history is without relation to the present subject.

Dog 72 (weight 10 kilos).

August 16, the splenic half of the pancreas was removed, leaving the duodenal half communicating with the main duct. There was no glycosuria, but polyuria up to 2500 cc., with specific gravity sometimes as low as 1002–1005. Just as true diabetes is often delayed till the second day after operation, so also was the polyuria in this case. The diuresis was so intense, and the urine so water-like, that on the first days it was measured only carelessly, the supposition being that water was spilled into it, especially as the water-cup was emptied so rapidly. But when the dog was observed to pass one specimen as water-like as the rest had been, he was tested by removing all water from the cage, and supplying it only at intervals, for drinking under observation. By this method, and by close personal observation, the polyuria was positively demonstrated. The quantity later diminished (about August 25), presumably because of the peritoneal abscess which was found in a secondary operation September 3.

Dog 48; bull-terrier; female; weight 9 kilos. Catheterized twice daily.

July 5, pancreatic tissue weighing 15.2 g. was removed, leaving a remnant estimated at 4 g. communicating with main duct. The urine was normal and scanty till July 9; then, without any food having been given since the operation, it rose to 965 cc. On the same day, feeding was begun, and the urine remained at over 1200 cc. daily, with specific gravity generally about 1010, never above 1018. Polyuria was present and glycosuria absent on both meat and bread diet. The condition persisted till the dog was killed in connection with another experiment on July 18. Autopsy showed peritoneal cavity in good condition, and the normal-appearing, hypertrophied pancreas-remnant weighing 7 g.

Dog 95; Toy Boston terrier; weight 6500 g.; very old; excessively fat. Not catheterized.

September 26, pancreatic tissue weighing 16.1 g. was removed, leaving a remnant estimated at 1.45 g. presumably communicating with lesser duct. Diabetes gravis was to have been expected under these conditions, but there was no sign of glycosuria. The urine remained normal till feeding was begun on September 30. The next day's urine was over 500 cc., and on the following days

varied from 500 to 800 cc., with specific gravity of 1007–1012. Appetite was normal but thirst excessive. The great obesity causes the body-weight to give a wrong impression; the dog was very small, and the quantity of urine stated represented a marked polyuria. During the early days of October, appetite failed and weight was rapidly lost; strength failed far more rapidly than in starvation, and this pancreatic cachexia brought death on October 8.

The following two dogs are of a different order from the preceding. These experiments concerning obliteration of the portal vein by the Bernard method must be considered with other similar experiments in Chapter XX. Some of the experiments in that chapter are suited to serve as control experiments, indicating that the effects here observed are not due to a foreign body surrounding the portal vein, nor to the infected sinus, nor to adhesions, or other accidental influences. They are perhaps due to a certain sort of circulatory disturbance in the pancreas. The degree of stasis seems to be a factor, as suggested in Chapter XX. Probably this is the reason why others have observed negative diuretic effects, or oliguria. Probably also this is the reason why De Filippi found polyuria in just one dog. Two positive results with no failures have led me to believe that with the same technique, uniform results may be possible.

The wire used to surround the vein is the ordinary sort for hanging pictures, and consists of a loose twist of small wires. Such wire therefore has bulk combined with flexibility. Its large size serves to make a little pressure on the vein, and obliterates it more quickly than small wire or thread, unless the latter is tied. The flexibility avoids danger of kinking the vein. Wire has the advantage over soft ligatures, that the dog cannot chew it. But it is more dangerous, and has caused several deaths for me; therefore I later made use of linen or silk, protecting the ends outside the body by braiding small wire into them. A binder might be employed, but the wound is kept cleaner when the dog licks it. The presence of the wire or ligatures, and even traction on them, are evidently painless.

Dog 73 [see protocol in Appendix].

On August 28, a loop of No. 3 picture wire was passed loosely about the portal vein without twist or knot, and the ends left

protruding outside the abdomen. Polyuria ensued, and increased till it was two or three litres per day, with specific gravity of 1004–1012. Glycosuria was absent on bread diet, though the dog ate enormously and grew fat, being all the time strong and lively. The wire came out on September 28, proving the vein obliterated. On October 3, a change to meat diet had little or no effect upon the urine; in particular, the specific gravity was not altered. October 9–11 the dog fasted, and during this time the urine was diminished in quantity, but was still far in excess of the excretion of a normal fasting dog, and the specific gravity remained low as before (1012 in last urine before operation, October 11). Death occurred on October 12, in consequence of partial pancreatectomy the day before. At autopsy the portal vein was found obliterated. The pancreas was normal to gross and microscopic examination, except for dilated veins and very prominent islands of Langerhans [see Chapter XXI, and Fig. 6].

Dog 167 [see protocol in Appendix].

On December 11, pancreatic tissue weighing 34.4 g. was removed, leaving a remnant estimated at 6.5 g. communicating with the main duct. One strand of fine wire, and another of heavy silk, were passed about the portal vein without tying, and the ends left protruding outside the abdomen. Feeding was begun December 15. The urine was slightly abundant all this time, but not abnormally so. The delay as compared with Dog 73 was possibly due to the fact that the ligatures about the vein were much smaller in bulk. On December 19, the first abnormal thirst was observed, with corresponding diuresis beginning the next day, and increasing. On December 27, the ligatures came out, proving the portal vein obliterated. The polyuria was not equal to that in Dog 73, possibly because infection ensued. Perhaps from some focus in the peritoneum or liver, metastatic abscesses developed, one in each hind leg. Recovery was complete. Polyuria continued even while the dog was seriously ill. The specific gravity of the urine was not affected by change of diet.

In the original operation, the pancreatic tissue left amounted to $\frac{1}{6}$–$\frac{1}{7}$ of the gland. The purpose was to determine whether the apparent diabetes insipidus, resulting from obliteration of the portal vein, was accompanied by any increased tendency to diabetes mellitus. Like Dog 73, this dog was able to live on bread without glycosuria. An increased tendency to diabetes

was therefore not present, since a smaller remnant ($\frac{1}{8}$–$\frac{1}{9}$ of the gland) ordinarily permits diabetes levis; the tolerance of this dog with a remnant of $\frac{1}{6}$–$\frac{1}{7}$ of the pancreas was the same as should be expected without obliteration of the portal vein. On January 12, additional pancreatic tissue weighing 2.1 g. was removed, and diabetes gravis developed, as in normal dogs. The subsequent history does not concern the present subject.

Conclusions.

Two questions require answers:

1. Is diabetes insipidus a disease of the pancreas?
2. Is diabetes insipidus a lack of amboceptor?

1. Is Diabetes Insipidus a Disease of the Pancreas?

At the outset, a question may be raised whether all cases of diabetes insipidus are identical, and whether the tests are yet sufficiently decisive to distinguish between the different possible forms of polyuria. Evidence suggestive of a relation between diabetes insipidus and the pancreas may be thought of as follows.

(*a*) A similar nervous basis as in diabetes mellitus, and similar exciting causes, of trauma, syphilis, etc. Hereditary disposition exists in both, and they sometimes occur in the same family.

(*b*) Transitions between insipidus and mellitus.

(*c*) Pruritus, cataract, bulimia, weakness, emaciation, etc., in diabetes insipidus.

(*d*) Diabetes insipidus associated clinically with lesions of the pancreas.

(*e*) Experimental production of diabetes insipidus by operations upon and about the pancreas.

None of this evidence should be over-estimated. Gout, nephritis, and insanity also sometimes run in the same family with diabetes mellitus. Transitions between insipidus and mellitus may be explainable by a similar diathesis. It seems possible that diabetes insipidus and diabetes mellitus may occur in the same patient; but the sugar-tolerance in pure diabetes insipidus is generally normal, and there is no evidence that the association with diabetes mellitus is anything but accidental. The symptoms under (*c*) are mostly nervous and prove nothing. The clinical reports of diabetes insipidus in connection with organic pancreatic lesions are somewhat suggestive; the fact that the

pancreas appears normal in most cases of diabetes insipidus is not very different from the rule in diabetes mellitus. The condition sometimes resulting from partial pancreatectomy is perhaps best designated as pancreatic polyuria. It is an interesting and suggestive condition, and the possible effects of pancreas feeding in connection with it may also be interesting; but it apparently does not meet the tests of true diabetes insipidus. It occurs only in a minority of cases of partial pancreatectomy, from unknown causes, and the fact that in several instances it was brought sharply to a close by the Bernard puncture may indicate a nervous origin, perhaps therefore of vasomotor nature, checked by the vasomotor effect of the piqûre. The cases of obliteration of the portal vein by the Bernard method are in a class by themselves. As far as convenient, the possibilities of a nervous origin from the foreign body, the infected sinus, etc., were excluded by control experiments. Under the conditions, it was considered not feasible to undertake experiments with salt, etc. It is not yet certain that this permanent form of polyuria is diabetes insipidus, or that it is of pancreatic origin. If either this or the clinical diabetes insipidus represents a disorder of the pancreas, it is evident that the disorder pertains to some function entirely distinct from the carbohydrate function. Inasmuch as it is possible sometimes to obtain pancreatic azoturia or cachexia without glycosuria and without extreme lowering of the sugar-tolerance, it is conceivable that suitable influences might produce a disturbance of a hypothetical salt-function of the pancreas without disturbance of the carbohydrate function. The facts do not warrant a conclusion. If the method described is found to produce this form of polyuria in all or most cases, it at least affords an opportunity for investigation, which may contribute information concerning diabetes insipidus or other conditions. This polyuria is more marked and permanent than most other forms of experimental polyuria that have been reported; it is very different from the oliguria generally observed in connection with portal stasis; and the possibility seems worth considering, that it may be due to some special circulatory condition in the pancreas.

2. Is Diabetes Insipidus a Lack of Amboceptor.

Reference has heretofore been made to the firm manner in which salts are bound, *e.g.*, in starvation, and the absence of any known chemical compound to account for such binding. If foods

are ordinarily fixed and assimilated by means of amboceptor substances, it is not unreasonable to assume such amboceptors for inorganic materials, such as salts and water; in fact, these materials of small molecule are the very ones which most evidently require some form of binding to permit their retention and prevent their escape. If diabetes insipidus is a disease of the pancreas, one of the possible hypotheses is that it consists essentially in a deficiency of amboceptor for certain substances, notably salts. It is not a necessary corollary that the pancreas is the sole source of such amboceptor. For the recognition of distinctions between free salt and combined salt, the only test yet available is that of diuresis, just as in the case of free sugar and combined sugar. I regret that I have not been able to carry out tests with salts similar to those with sugars. Forschbach and Weber have found that sodium chloride, taken by mouth, is a far more active diuretic in diabetes insipidus patients than in other persons. Like other authors, they have sought the cause in a heightened "sensitiveness" of the kidney. But the kidney in diabetes insipidus is not thus "sensitive" toward other substances. For example, in Meyer's experience, theocin caused some actual concentration of urine (though Seiler failed to confirm). Also, in Meyer's experience, sodium phosphate is excreted without increase of diuresis in diabetes insipidus just as in the normal state. When the supposed "sensitiveness" of the kidney is limited to one or to a few substances, it is permissible to inquire whether the alteration is actually in the kidney, or whether it may be in these substances. Any alleged "sensitiveness" of the kidney to sugar is easily ruled out in diabetes mellitus, by the fact that dextrose given intravenously is a diuretic in normal just as in diabetic animals, though in the normal there is a secondary oliguria, after the sugar has become combined. Furthermore, other sugars show practically unchanged diuretic activity in diabetes. A similar series of tests will perhaps help to decide the questions raised for diabetes insipidus. Comparisons may be interesting between salt given by mouth, subcutaneously and intravenously; comparisons between the latter two methods may be specially valuable. Physiological saline injected subcutaneously is surprisingly slow in increasing the urine, according to my few experiences with normal dogs [Chapter VI]. Sodium chloride is never an anti-diuretic; even its combined form, if there is one, must possess diuretic properties, perhaps because of the smaller molecule or looser binding. But

it may be interesting to learn whether the comparative effects of this salt orally, subcutaneously, and intravenously are the same in diabetes insipidus patients as in normal persons, and if there is a difference, whether it is demonstrable with other salts or only with this one. Animals such as Dogs 73 and 167 may perhaps also furnish material for study.

In general, there seems to be ground for believing that diabetes insipidus belongs among the disorders of internal secretion. If diabetes insipidus is frequent with hypophyseal trouble, so also is diabetes mellitus; and the latter is a disease of the pancreas. Diabetes insipidus occurs without signs of hypophyseal disorder. Disturbances of internal secretion frequently involve more than one gland, and it may be difficult to say which produces a given effect. There is perhaps as clear a connection, through clinical and experimental evidence, between the pancreas and diabetes insipidus as between the hypophysis and diabetis insipidus. The facts are not yet sufficient to warrant a conclusion or hypothesis. It is hoped that the above suggestions may prove of some value for future investigation.

CHAPTER XII.

CLASSIFICATION OF GLYCOSURIAS.

THE purpose of this and the few chapters immediately succeeding is primarily to establish the relations between diabetes mellitus and certain well-known glycosurias. For this purpose, two methods are proposed.

(1) The application of the tests of diabetes to these other glycosurias. Not only the true nature of these glycosurias, but also the validity of the tests, will be thus established.

(2) The production of various glycosurias in animals on the verge of diabetes as a result of partial removal of the pancreas. This was one of the primary purposes of the entire research. If a given glycosuric agent tends toward diabetes, it may be able to cause true diabetes in an animal thus on the verge. Such an animal corresponds to the human patient with weakened pancreatic function; the glycosuric agent corresponds to the exciting cause of diabetes. The failure of experimenters who have tried to produce a functional as opposed to an organic diabetes mellitus in animals, may be due to the use of normal instead of predisposed animals.

Known forms of glycosuria are so numerous, and their causes so varied, that some kind of classification is highly desirable. The need for classification has been felt, but imperfect knowledge long interposed difficulties. Even now that information is more adequate, the complexity of the subject remains as a serious obstacle. Classifications used in texts, as those of Naunyn, von Noorden, Lepine, and Pflüger, and in current reviews, as by Glaessner (2) and by Garrod, amount to little more than a simple enumeration. Easily the best classification yet presented, and one which possesses permanent value, is that of Pollak (2). With one slight change (based on Starkenstein's (3) evidence concerning asphyxia), Pollak's classification is as follows.

A. GLYCOSURIA RESULTING FROM RENAL ACTION:

(*a*) Without hyperglycemia: phloridzin.

(*b*) With or without hyperglycemia: renal poisons.

B. Glycosuria Resulting from Hyperglycemia:

(*a*) Independent of glycogen-content of organs: diabetes.

(*b*) Dependent upon glycogen-content of organs, and caused by sympathetic stimulation:

(1) Central (analogous to piqûre): caffein, strychnin, asphyxia, stimulation of sensory nerves.

(2) Peripheral: adrenalin.

Pollak's table concerning the relations of different glycosurias to blood-sugar, liver-glycogen, cutting of splanchnics, etc., is also a useful contribution.

For various reasons, a different form of classification will be attempted here. For one thing, the subject of glycosuria is so complex that several classifications may be found convenient, each according to a particular point of view. Since most forms of glycosuria are dependent upon the liver and its glycogen, while certain forms persist after extirpation of the liver, a distinction is possible from this view-point between "liver-glycosuria" and "muscle-glycosuria." A "muscle glycosuria" is claimed, correctly or otherwise, to be produced by the following agents: cold [Loewit], curare [Langendorff (2)], intravenous salt injection [Wilenko (3)], vagus stimulation [Bang, Ljungdahl and Bohm]. The concept of "toxic" glycosuria is also valuable, and the term must necessarily sometimes be used. Garrod (1) thus sets apart a "toxic" group, and it includes such a heterogeneous assembly as curare, uranium, phloridzin, anæsthetics, thyroid, and adrenalin. Caffein, etc., might have been included, and there is a question whether the glycosuria of infections and of pregnancy is not properly "toxic." This grouping is useful in that it plainly classifies adrenalin and thyroid as toxic glycosurias, and withdraws them from relation with diabetes. Pollak has made the blood-sugar the central feature in his scheme. This is one useful basis of arrangement, especially from some points of view. But every classification has also its faults, and criticism of Pollak's grouping is not difficult. The number of glycosurias without hyperglycemia is so small as compared with those with hyperglycemia, that Garrod has remarked that this distinction is like dividing mankind into those who are albinos and those who are not. Also, hyperglycemia as the chief wall of division breaks down at a number of points; the distinctions based on it are sometimes slight or absent; while on the other hand, funda-

mental differences, such as mark off diabetes mellitus, are relegated to a secondary position. My own arrangement will also inevitably be open to criticism, but it is hoped to make it first, complete, and second, convenient.

It is possible to divide glycosuria into *alimentary* and *spontaneous;* and any spontaneous glycosuria may be regarded as due to some influence exerted upon one of four organs:

Pancreas.
Liver.
Kidney.
Nervous system.

This scheme when expanded becomes the table on following page.

Some of the doubtful members on the list are indicated by interrogation points. In a number of respects, information is still needed; but errors can easily be corrected by a simple rearrangement. Additions to cover possible omissions are equally easy. The *direct* action of the causes is the basis of classification; some influences cause glycosuria by an action directly upon the liver, kidney, or pancreas; other influences have no direct action upon these organs, but their direct action is upon the nervous system. These nervous forms of glycosuria are a sufficiently distinct and important group to warrant fully the major position assigned to them. Also, the arrangement generally refers to the essential or most important action of the cause. Thus certain renal poisons produce hyperglycemia, by an effect upon the liver either directly or through nervous stimulation; but yet the direct effect upon the kidney is most important for the glycosuria. In a few cases, repetition has been made to include several known or possible effects of the same agent. Foreign sera apparently act upon both liver and kidney (possibly also nervous system). Diuretic drugs are said to cause glycosuria chiefly through hyperglycemia resulting from central nervous stimulation; yet an effect upon the kidney should not be forgotten. It is not feasible to follow this contributory renal element through all forms of glycosuria, though frequently it is important. Thus, piqûre and adrenalin cause glycosuria chiefly through a nervous effect upon the liver; but both have also a diuretic effect, and the result of their action upon the kidney is a far greater excretion of sugar than is caused by the same degree of hyperglycemia under other conditions, *e.g.*, in alimentary glycosuria. The classification

CAUSES OF GLYCOSURIA.

- 1. Alimentary...
  - A. Normal. — Due to over-doses of sugar orally, subcutaneously, intravenously, etc.
  - B. Pathological.
    - I. Due to general malnutrition....
      - (a) Hunger glycosuria of dogs.
      - (b) Vagabond glycosuria.
      - (c) "Dyspeptic" glycosuria.
      - (d) Cachectic glycosurias.
    - II. Due to any of the causes of spontaneous glycosuria.
- 2. Spontaneous...
  - A. Pancreas.... (Organic disease / Functional disease.) Diabetes mellitus.
  - B. Liver.....
    - I. Hemorrhage.
    - II. Injections into portal vein.
    - III. Poisons.....
      - (a) Drugs.
      - (b) Animal products(?).
      - (c) Pregnancy (?).
    - IV. Infections (?).
    - V. Asphyxia (?).
    - VI. Traumata (?).
  - C. Kidney.....
    - I. Glycosuria due to increased permeability to blood-sugar.
      - (a) Diuretics (?).
      - (b) Specific renal poisons (cantharidin, metallic salts, etc.).
      - (c) Sera and organ extracts.
      - (d) Renal injuries.
      - (e) Clinical renal glycosuria.
    - II. Glycosuria due to breaking up of abnormal compounds.
      - (a) Phloridzin.
      - (b) Glycogen, dextrin, starch (and in dogs cane-sugar) (?).
  - D. Nervous system...
    - I. Central.....
      - (a) Piqûre, experimental brain lesions, clinical brain troubles.
      - (b) Emotions.
      - (c) Asphyxia (including asphyxial drugs).
      - (d) Nerve-poisons.
      - (e) Salt injections.
      - (f) Irritation of afferent nerves.
      - (g) Cold.
      - (h) Fever.
      - (i) Infections.
      - (j) Fatigue (?).
    - II. Peripheral.....
      - (a) Stimulation of splanchnic nerves.
      - (b) Adrenalin.
      - (c) Drugs and poisons (?).
    - III. Undetermined...
      - Thyroid.
      - Parathyroid.
      - Hypophysis.
      - Ligature of thoracic duct (and clinical chyluria (?)).
      - Pregnancy (?).
      - Tumors (?).

presented is confined to glycosuria. Levulosuria, maltosuria, and other anomalies have no place in it. The various members of the series will now be discussed in order.

1 A. Normal Alimentary Glycosuria.

This necessarily results from excessive doses of sugar, and from no other food. The sugar may be given not only by mouth but by any of the possible channels. The subject of tolerance has been sufficiently treated in Chapter I.

1 B. Pathological Alimentary Glycosuria.

This refers to any lowering of the normal carbohydrate tolerance. The glycosuria may result from doses of sugar below the 100 g. chosen as the arbitrary clinical standard, or it may come from starchy food. The causes of the lowering of tolerance naturally fall into two groups.

I. Alimentary Glycosuria Due to General Malnutrition.

(*a*) *Hunger Glycosuria of Dogs.*

Claude Bernard discovered that dogs which suddenly received a large carbohydrate meal after long fasting often showed glycosuria, which quickly disappeared with continuance of the feeding. Lehmann is said to have studied the subject in 1873. The best known work is that of Hofmeister (2). Dogs starved for periods varying with the individual susceptibility became subject to very easy alimentary glycosuria. The dextrose tolerance was reduced from about 5 g. per kilo to 2 g. or even 1.3 g. per kilo. (These values have been discussed in Chapter I.) Starch feeding likewise caused glycosuria, in dosage of 5 g. per kilo, more or less. The glycosuria appeared 1 to 3 hours after feeding, and was generally slight; but in one instance the sugar excreted amounted to about one-third the ingested starch. By suitable under-nutrition, a slight glycosuria could be kept up for days and even weeks; but it could not be made permanent. It disappeared on abundant feeding with carbohydrate, and especially, always disappeared as soon as even small quantities of meat were added to the diet.

(*b*) *Vagabond Glycosuria.*

Hoppe-Seyler (1*A*) described a glycosuria sometimes observed in tramps and other poorly nourished patients soon after entrance into a hospital. Generally it is slight (0.5–0.7 per cent), but in one case reached 3.5 per cent. One patient was without alcoholic history. Most of them showed signs of liver-trouble (cirrhosis, or congestion due to heart lesions). The sugar was found generally only on the first day. While present, it could be increased by abundant carbohydrate feeding, but disappeared quickly with improved nutrition, irrespective of the kind of diet.

(*c*) "*Dyspeptic*" *Glycosuria.*

Some authors, especially French, recognize a "dyspeptic glycosuria." The excretion is very slight, and occurs only during the period of digestion. Robin found glycosuria 83 times among 1600 cases of gastro-intestinal disorder. In Chapter V, mention was made of the slight glycosuria which sometimes occurs in babies with severe nutritional disorders. Cobliner (1) found that in such babies, the sugar content of the blood is not increased. Rosenberger is a believer in gastro-intestinal glycosuria, and reviews the literature exhaustively. Persons are mentioned in whom every attack of indigestion produced a slight glycosuria, especially after certain foods for which there was an idiosyncrasy.

(*d*) *Cachectic Glycosuria.*

Under this title may be grouped a few rare cases somewhat analogous to the above types. Extreme *fatigue* is supposed by some authors to cause a slight temporary glycosuria. It is doubtful if any such spontaneous sugar-excretion (aside from inosituria) results from fatigue; but it would not be surprising if there were an increased tendency to alimentary glycosuria, due to impaired ability of the exhausted body-cells to use or store sugar. *Senile* glycosuria is probably due generally to renal causes; but there is evidence for a form of easy alimentary glycosuria in the very old, due to diminished power of senile cells to utilize sugar. [See Aldor.] Likewise, spontaneous or alimentary glycosuria may be present to the extent of traces in carcinoma, tuberculosis, Addison's disease, leukemia, liver diseases, and similar cachectic states. Both weakness and intoxication are doubtless responsible; but the effect is probably a general one, upon the entire body, and not

traceable to any single organ. To some extent, the glycosuria *ex amylo* of fever and of alcoholism belong in this category.

II. Alimentary Glycosuria Due to Other Causes.

Any of the causes which, in sufficiently high degree, can produce spontaneous glycosuria, will when active in less degree lower the tolerance for ingested carbohydrate. Ingested carbohydrate acts here as a second cause of glycosuria. Rarely, two causes of glycosuria counteract each other so that no glycosuria results; but the almost universal rule is that two causes of glycosuria, each not quite able to cause glycosuria alone, will suffice for glycosuria when acting together; or glycosuria due to one agent will be increased by some other agent. Underhill (4) has furnished such an illustration in paraldehyd and adrenalin, and Starkenstein (3) has followed up the idea. By going down the list of pancreas, liver, kidney, and nervous system, and their subdivisions, it is possible to classify any case of alimentary glycosuria due to specific disorder anywhere in the body.

2 A. Pancreas.

Diabetes mellitus is invariably a disease of the pancreas. Previously, there was offered a division of diabetes on the basis of severity, viz., into *diabetes gravis* and *diabetes levis*. The present classification is one of etiology; therefore we must distinguish diabetes due to organic lesions from diabetes due to functional disorders. The separation is not absolute, and is becoming less distinct as the study of the finer microscopic alterations of the gland progresses. Nevertheless, it is not yet possible for the pathologist with his microscope to diagnose all cases of human diabetes, and in a large proportion of patients the pancreas at autopsy appears absolutely normal to our present methods of investigation. Some changes found are doubtless secondary. It is therefore necessary to recognize a purely functional pancreatic disorder as the basis of cases of human diabetes.

The classification properly brings out the difference between the position of the pancreas and that of other organs, such as the thyroid, parathyroid, adrenal, and hypophysis. These organs or their secretions can act only upon the nervous system, and the nervous stimulation may then give rise to glycosuria by action especially upon the liver; they therefore belong under the causes

of nervous glycosuria. The pancreas does not act through the nervous system, nor upon the liver more than upon other tissues. The disordered function of the gland itself, through deficiency of amboceptor, is the cause of glycosuria. A primary position is thus won for it; causes may produce glycosuria by direct action upon the liver which supplies sugar, or upon the kidney which excretes sugar, or upon the pancreas which supplies amboceptor. Direct action upon no other organ produces glycosuria, so far as known; *e.g.*, "muscle-glycosuria" is presumably produced through the nervous system. All causes of glycosuria not affecting the liver, pancreas, or kidney directly, have their direct action only upon the nervous system.

2 B. Liver.

The group of hepatic glycosurias here is not the same as that of von Noorden and some other writers, who use the term to cover all forms in which the sugar is derived from the glycogen of the liver. Such a classification could be of service only for distinction between "liver" glycosuria and "muscle" glycosuria, and its application is limited. In the great majority of glycosurias, most or all of the surplus sugar is furnished by the liver, and nervous agencies in particular act preëminently upon the liver. A separate group of "liver" glycosurias is important, but it must be limited to those in which our present knowledge indicates that the causative agent acts directly upon the liver cells.

I. Hemorrhage.

The hyperglycemia resulting from hemorrhage is well known, though generally it does not suffice for glycosuria. Nishi (1) found that neither double splanchnicotomy nor double epinephrectomy prevents the increase of blood-sugar following repeated bleedings. The former rules out a central nervous cause. And since the excitability of local nervous mechanisms is so greatly lowered after loss of both adrenals, it is safe to conclude that the latter rules out a peripheral nervous cause. Nishi's deduction that hemorrhage acts by a direct effect upon the hepatic cells is therefore justified.

II. Injections into Portal Vein.

Injections into the portal vein readily cause a breaking down of liver glycogen. Claude Bernard named several substances

which have this effect. Harley is cited by Lepine [(1), p. 332] as having found that a very small quantity of alcohol thus injected causes glycosuria, though simple ingestion of even large quantities of alcohol is only exceptionally followed by glycosuria. Chloroform and ammonia behaved similarly. Jardet and Niviere caused glycosuria in rabbits by injecting 100 cc. 3 per cent HCl into a mesenteric vein. Lepine [(1), p. 333] obtained glycosuria by injecting a few cubic centimeters of saliva into a mesenteric vein. Pariset [Thèse Paris, 1906, also (1) and (2)] caused hyperglycemia by injecting a few cubic centimeters of pancreatic juice into the portal vein. Secretin injected into the portal vein was found by Pariset (3) to have no such effect. Tuckett (1) produced glycosuria as high as 9 per cent in cats by injection of lymph into the splenic vein; and simple injection of a few bubbles of air into this vein caused glycosuria of 3–4 per cent. It is safe to assume that a very long list of substances would act similarly, through a direct injurious effect upon the liver. But [see Chapter XX] the claim of several authors, that arterial blood entering the portal vein causes glycosuria, is probably incorrect.

III. Poisons.

(*a*) *Drugs.*

The effects of portal vein injections establish the possibility of glycosuria from direct poisoning of the liver, and the assumption of direct action is made probable by anatomic alterations produced by some drugs in the liver, presumably not by nervous means. Phosphorus and arsenic in exceptional instances cause glycosuria; and since their action is largely upon the liver, the glycosuria may perhaps be due to a sudden dropping of glycogen by the poisoned hepatic cells. In rare cases of acute yellow atrophy a slight glycosuria may be found, due perhaps to direct action of the unknown poison. Ether must be given a positive place in the list of substances which directly affect the liver, according to the experiments of King, Chaffee, Anderson and Redelings. The subject has been studied further by King, Moyle and Haupt with intravenous injections of ether; they were thus able to produce hyperglycemia and glycosuria without asphyxia. A similar direct influence is imaginable as a secondary effect of many of the other drugs to be later enumerated, which cause glycosuria primarily by action upon the nervous system or kidney.

(*b*) *Animal Products.*

Foreign serums, organ-extracts, albumins, etc., are a class of poisons which are known to act directly upon the liver. In some respects, the action upon the liver is more intense than upon the nervous system. For example, Jackson and Pearce have described the liver-necroses produced by injections of hemolytic sera; but we know of no corresponding nervous lesions. Since in other respects the action upon the liver may predominate, it may conceivably play a part as respects glycosuria.

Tuckett (1) found that if thoracic lymph from a fasting dog is injected into the portal circulation of a cat, no hyperglycemia or glycosuria results; but if lymph from a digesting dog is thus injected, the result is hyperglycemia of 0.3 to 0.9 per cent and glycosuria from 1 to 9 per cent. The thoracic lymph of a digesting cat injected into its own splenic vein causes glycosuria of over 2 per cent. The phenomena are apparently toxic.

Dufresne (ref. by Kleen, p. 58) observed glycosuria after injections of pancreatin. Pariset (1 and 2) caused hyperglycemia and glycosuria by intravenous injections of pancreatic juice. Leschke (1) increased the glycosuria of diabetic animals, and produced slight glycosuria in non-diabetic animals, by subcutaneous or intraperitonal injections of pancreatic extract. This glycosuria is of non-specific, toxic character, and is possibly due to direct effects upon the liver. The same is true of the slight glycosuria produced by occasional investigators in animals by injections of diabetic urine or extracts of diabetic feces, intestinal contents, or organs. The exact mechanism is unknown; the direct action may perhaps be upon liver, kidneys, or nervous system; at any rate it is a simple toxic glycosuria with nothing specific or diabetic in its nature.

Hibbard and Morrissey reported occasional slight glycosuria from diphtheria antitoxin.

De Meyer (2) claimed to have produced an anti-glycolytic serum, which hinders glycolysis in blood or exudates to which it is added, and on intravenous injection causes hyperglycemia and glycosuria, supposedly from inhibition of glycolysis. Also, De Meyer (6 and 7) claimed to have produced an anti-pancreatic serum, by heating dog-pancreas at 70 degrees for half an hour to kill the ferments, and then injecting into rabbits. The serum of such rabbits, injected into dogs, is alleged to produce slight

hyperglycemia but a somewhat greater glycosuria, to change the permeability of the kidney for sugar, and to cause specific changes in the islands of Langerhans. Rinderspacher repeated De Meyer's work, and pointed out errors which invalidate it, along with the fact that any hemolytic serum may cause glycosuria. Ssobolew (3) undertook to obtain islet-tissue as free as possible from other parenchyma by ligating the ducts in rabbits; after 4–6 months the atrophied pancreas-tissue was injected into guinea-pigs, and the serum of the latter, after several such injections, was used for injection into rabbits. Results were entirely negative. [See also Sauerbeck, p. 626.] Ssobolew furthermore reports similar experiments by Klimenko, who injected atrophied pancreas-tissue of rabbits (1 year after ligating ducts) into dogs, and found the serum without specific cytotoxic or glycosuric effect. In addition to these negative findings, the following reasons stand against De Meyer's claims: (1) Anti-sera for individual organs cannot be produced. (2) As Biedl [(3), p. 16] has stated, "hormones" are never antigens. (3) The character of the glycosuria claimed is not that of diabetes. The glycosuria obtained by De Meyer is evidently of non-specific, toxic nature.

(*c*) *Pregnancy.*

Not only lactosuria (formerly mistaken for glycosuria), but also true glycosuria, may be found during pregnancy and childbirth. Lepine [(1), p. 321] refers to statistics showing that 40 per cent of pregnant women show glycosuria at some time. Von Noorden [(1), p. 211] quotes Reichenstein's estimate of 10 per cent. Garrod (3) gives some case-histories and a discussion. Reichenstein (1) found glycosuria frequent in pregnant women after 100 g. dextrose. A recent and excellent paper is by Schirokauer (3), with a review of the literature; he demonstrated normal blood-sugar values throughout pregnancy, and after ingestion of 100 g. dextrose a hyperglycemia not in excess of that of normal persons. The finding by Neu [ref. by von Noorden, (1), p. 121] of increased adrenalin in the blood during pregnancy offers no explanation of the glycosuria of pregnancy, for the following reasons: (*a*) Bröking and Trendelenburg have proved that the adrenalin content of the blood in pregnancy is normal. (*b*) The glycosuria generally occurs only toward the end of pregnancy. During most of the period of the alleged adrenalinemia, the sugar-content of the blood is normal. (*c*) Long-continued excess of adrenalin produces

"immunity," as proved by repeated injections. The occasional glycosuria toward the end of pregnancy is therefore probably not the result of months of adrenalin excess.

The hypophysis is thought of by some as the cause of the glycosuria, but this assumption rests only upon the interesting anatomical findings in the gland, which shows marked and typical hypertrophic and secretory changes during pregnancy (Cushing). But these changes do not necessarily have anything to do with glycosuria or carbohydrate metabolism, and conservatism is the safest attitude at present, with skepticism. The thyroid is a possible factor. The slight intoxication in pregnancy is probably a cause of the glycosuria, and with it is associated the abnormal nervous state. It is unknown whether these influences affect chiefly the liver, kidneys, or nervous system. A direct influence upon the liver is one possibility, but a nervous mechanism would seem to be most probable. A latent diabetes may be brought out by pregnancy. Except in such cases, tests will doubtless show that the paradoxical law and anti-diuretic action of dextrose still hold good.

IV. Infections.

Glycosuria is occasionally found in a large variety of infectious diseases. These will be considered in connection with the nervous system. The possibility exists that direct injury of the liver is a contributing cause in rare acute cases.

V. Asphyxia.

Asphyxia and asphyxial drugs cause glycosuria by central nervous action. In a high degree of asphyxia, a direct action upon the liver is imaginable. Bing pointed out that stasis of the liver produced in obtaining blood is the greatest source of error, in experiments claiming to prove a higher sugar-content in the hepatic than in the portal blood. Macleod (2) showed that rapid glycogen break-down begins if the portal vein is clamped for 2 minutes. Macleod and Ruh showed that glycogenolysis is still more highly stimulated if the hepatic artery as well as the portal vein is occluded. Local stasis and asphyxia are positive as causes of sugar-formation. There is a possibility that stasis and asphyxia due to general causes may have some secondary local effect. The question is then open whether this local effect is a direct action upon the liver-cells, or upon some peripheral nervous mechanism.

Neubauer (4) has lately reported hyperglycemia and glycosuria produced by clamping the hepatic veins and subsequently releasing the clamp. Also, by plethysmographic investigation of the liver, he found that the organ becomes enlarged and hyperemic after piqûre or intravenous injection of adrenalin. Another pressure-raising substance, barium chloride, showed the same effect upon the liver, and also produced a slight glycosuria, though the glycosuric was close to the lethal dose and results were irregular. Anæsthetics such as chloral hydrate and alcohol inhibit both the vascular effect and the glycosuria. Morphine or pantopon has very little effect. The fact that piqûre causes increased blood-pressure, altered breathing, and excretion of sarcolactic acid in the urine causes him to rank this among the asphyxial forms of glycosuria.

Almost simultaneously, Masing has found, in perfusions of "surviving" rabbit livers, that cold, diminished oxygen access, or adrenalin produce increased sugar-formation. Other agents, such as $BaCl_2$, $MgCl_2$, formol, and As_2O_3, diminish the circulation but do not thus increase sugar-production. The inhibition of sugar formation produced, for unknown reasons, by As_2O_3 is particularly marked. Adrenalin impairs oxidation by constricting the vessels; the venous flow becomes very scanty and dark; later dilatation occurs, while utilization of oxygen still remains deficient. After HCN or formol, adrenalin no longer alters circulation and oxidation in this manner, but still increases sugar-production.

Accordingly, Masing's results, especially the last-mentioned, also those with barium chloride, overthrow some of Neubauer's ideas concerning the rôle of asphyxia. All the experiments are interesting, but the following facts should be borne in mind. (*a*) The concentration of adrenalin used by Masing (1 mg. to 300 cc. blood) is out of proportion to any quantity that could be present in the body even under the most abnormal conditions. The reaction of the liver to more moderate concentrations of adrenalin was found by Starkenstein (3) to be absent after death. It is possible that Masing's work concerns some direct cellular injury, different from the physiological effect of adrenalin, which is upon a peripheral nervous mechanism. No specific effect of adrenalin upon carbohydrate metabolism is demonstrated, and the greatest interest of the experiments is to invalidate Neubauer's ideas concerning the simple asphyxial action of adrenalin. (*b*) The observation concerning arsenic is interesting, in view of

the power of arsenic, glycerin, and other substances to inhibit glycosuria after piqûre. (*c*) Piqûre and adrenalin glycosuria cannot be explained as asphyxial. No form of asphyxia ever produces such an intense glycosuria as these two agents may. Asphyxia does not produce a sugar-excretion in excess of the glycogen-content of the liver. Neubauer used intravenous injections of adrenalin, which give maximum circulatory and minimum glycosuric effects. Had he used subcutaneous injections, glycosuria would presumably have been greater and the circulatory changes in the liver less. (*d*) Asphyxial glycosuria stands in no possible relation with diabetes. The deficient intensity is one reason. Also, liver-asphyxia to the point of glycosuria could not exist for months and years without demonstrable changes in the liver. But especially, the nature of the process itself should be borne in mind. Asphyxia, like numerous other injuries, may cause glycogen-containing cells to discharge their glycogen as sugar. But the problem of diabetes is why cells should continuously form and discharge sugar, even in excessive amount. This active new-formation of carbohydrate to be discharged is altogether different from anything produced by asphyxia or similar non-specific injuries. (*e*) Neubauer's valuable observation concerning opium constitutes one more distinction between diabetes and these non-diabetic forms of glycosuria.

VI. Traumata.

Various direct injuries of the liver may cause a slight glycosuria. Naunyn (p. 56 ff) cites authors who found disappearance of liver-glycogen, also in some cases glycosuria, after ligature of the bile-duct. Some of the earlier claims were overthrown by Reuss, who found that this operation does not always cause glycogen-loss, and that piqûre is frequently successful after it. Naunyn also shows that glycosuria is absent in human cases of icterus and biliary stasis. Kleen (p. 49) refers to Claude Bernard as having caused glycosuria by ligation of the portal vein in the dog, also to Andrat, and to Colrat and Couturier, as having observed glycosuria in human pylethrombosis. Gall-stone attacks are sometimes accompanied by glycosuria, but not in the majority of cases. The conclusion is justified that glycosuria from direct traumatism of the liver is possible but rare.

No place is assigned to diseases of the liver among the "hepatic" causes of glycosuria, for the reason that diseases of the liver

do not cause glycosuria. It is thoroughly established, especially by Strauss, that hepatic disease is not characterized by either spontaneous or alimentary glycosuria. Naunyn (p. 58) and Saundby have set apart a group of "hepatic" diabetes, but the relation is non-specific. Even in "bronzed" diabetes the specific origin of the glycosuria is probably not in the liver. A clear conception concerning hepatic glycosuria may be that a healthy liver containing considerable glycogen may, when suddenly injured, discharge its glycogen so suddenly as to cause glycosuria; but chronically sick liver-cells do not of themselves perform the unnecessary work of building up glycogen and breaking it down in excessive quantity. Whenever a prolonged glycosuria of hepatic origin exists, its cause is nervous. Claude Bernard's observation of a sugar-puncture followed by glycosuria for a week is a case in point.

2 C. Kidney.

The classification of renal glycosuria predicates two distinct types. In one, the source of the urinary sugar is the blood-sugar, and glycosuria is due essentially to increased permeability of the kidney. These forms of glycosuria, unless accompanied by hyperglycemia, are always slight. In the second type, the normal blood-sugar is not the source of the urinary sugar, but the latter is derived from abnormal circulating compounds which are broken up by the kidney. Certainty concerning this subject is of course not yet attained. The classification represents that interpretation of the evidence which seems to me most probable; and if it proves incorrect, a rearrangement will be necessary.

I. Glycosuria Due to Increased Permeability to Blood-Sugar.

a. Diuretics.

Diuretic drugs are now considered to cause glycosuria chiefly through hyperglycemia produced by central nervous stimulation. This is in opposition to the early opinion of Jacobi, who thought that in caffein and diuretin glycosuria in rabbits he had found an experimental analogue of the "renal diabetes" of man. Richter (2) and also Rose proved that hyperglycemia accompanies these forms of glycosuria, and Pollak (2) and likewise Nishi (1*A*) proved the central nervous origin. Neumann (1) claims to have observed glycosuria after administration of diuretin in human patients, but

he is contradicted by von Noorden [(3), p. 530] and by Strauss. Mere polyuria as a cause of glycosuria has been overthrown; *e.g.*, in diabetes insipidus and in some normal individuals, intense diuresis may bring out a trace of inosit, but not glucose. Nevertheless, diuretic agents are a factor in glycosuria. First, they increase the sugar-excretion due to hyperglycemia. The different vascular and diuretic effects of adrenalin subcutaneously and intravenously are supposed to explain some of the difference in glycosuria between the two methods. Authors are agreed that all agents produce greater sugar excretion when diuresis is provided for. Second, diuretics assist in causing glycosuria, when the hyperglycemia in itself is not sufficient to produce it. Lützow found, in human patients, that doses of caffein or diuretin which alone do not cause glycosuria, and doses of dextrose (50–100 g.) which alone do not cause glycosuria, do produce glycosuria when given together. In the simple laboratory glycosurias from diuretic agents, it is probable that in many cases the hyperglycemia, though present, would give rise to little or no glycosuria except for the accompanying diuretic effect. Third, diuretics appear sometimes to cause glycosuria with normal blood-sugar. To this extent, the original claim of Jacobi is confirmed. Even Nishi (1*A*), in proving the nervous and hyperglycemic basis of diuretin glycosuria, saw in one animal glycosuria with glycemia of 0.125 per cent, not a specially high value for the rabbit. Underhill and Closson (1) state that intravenous injection of salt solution increases the permeability of the kidney to sugar, causing glycosuria in rabbits when there is no hyperglycemia. It is therefore certain that diuretic agencies can play some part in the production of glycosuria. The process may be an increased excretion or a diminished resorption [Nishi (3), Lepine (7)].

(*b*) *Specific Renal Poisons.*

Specific renal poisons are known to be a cause of primary renal glycosuria. Hyperglycemia may accompany, from an action upon the liver or nervous system; but altered permeability of the kidney is the essential condition.

The discovery of uranium glycosuria is credited by Claude Bernard to Leconte. It was studied by Chittenden and Lambert, by Woroschilsky, by Cartier, and by Meyner. [For other names see Kleen, p. 54, footnote.] Albuminuria accompanies glycosuria. Cartier found intense degenerative changes in the liver, hence it

is possible that hyperglycemia, when present, may be due, at least in part, to direct action upon the liver. According to Chittenden and Lambert, the glycosuria is dependent upon a supply of liver-glycogen. Lepine and Boulud (2*A*) and after them Blanck found absence of hyperglycemia during the glycosuria. Fleckseder found hyperglycemia present. Hyperglycemia is however not essential. Pollak (2) proved that cutting the splanchnic nerves does not prevent uranium glycosuria. The glycosuria is generally slight, but Lepine reports as high a figure as 1.4 per cent. In the recent work of MacNider, polyuria was found to accompany the glycosuria.

Glycosuria in the nephritis caused by chromic acid and its salts, especially potassium bichromate, has been studied by Veron, Pal (1), Blanck, and Kossa (2*A*). Kossa used both dogs and horses. Lohr has reported a case of human poisoning with glycosuria. Chromium glycosuria may exceed 1 per cent, but is generally slight. It is accompanied by albuminuria. Kossa and Blanck found the blood-sugar only 0.1–0.13 per cent. Pollak (2) found hyperglycemia present with uranium glycosuria. It is presumably dependent upon liver-glycogen.

Mercurial poisoning may cause more or less glycosuria with albuminuria. Kleen (p. 53) names a list of those who have observed it. Schröder and Graf wrote dissertations on the subject. Graf found no increase of blood-sugar. Richter observed an increase. Graf showed the glycosuria to be dependent upon liver-glycogen.

Richter (2*A*) proved that small doses of cantharidin injected subcutaneously cause glycosuria in rabbits, and that it depends upon a supply of liver-glycogen. Lepine [(1), p. 289] found hyperglycemia absent.

Salts of lead are said sometimes to cause glycosuria, and the same is doubtless true of salts of other heavy metals, and of a list of other substances which sufficiently injure the kidney. At the same time, the opposite effect must be remembered. Tachau (1), after 100 g. dextrose by mouth, repeatedly found marked hyperglycemia in human patients with chronic lead-poisoning, without glycosuria.

Glycosuria has occasionally been observed by Kossa from salicin, arbutin, amygdalin, coniferin, hesperidin, esculin, viridin, and saponin. The question is perhaps open whether these glucosides act entirely upon the kidneys, or upon the liver, or whether they should be added to the list of asphyxial drugs to be named later.

(*c*) *Sera and Organ Extracts.*

Sera, organ extracts, and other toxic biological products are known sometimes to cause hyperglycemia when injected; but it is also asserted that glycosuria may occur without increase of blood-sugar. Lepine [(1), p. 292] and Lepine and Boulud (3) report such experiments. Alcoholic extracts of liver, muscle, spleen, pancreas, and asphyxial blood, evaporated to dryness and dissolved in water, were injected into dogs. Repeated tests of blood-sugar showed uniformly normal values, yet the excretion of dextrose amounted to 3 g. or more.

(*d*) *Renal Injuries.*

Glycosuria with normal blood-sugar has been described by Lepine after the kidneys had been injured by ligation of the ureters for several hours. The slight glycosuria which may occur in cases of renal hemorrhage is mentioned especially by Naunyn, as also the glycosuria sometimes accompanying chyluria (see below).

(*e*) *Clinical Renal Glycosuria.*

Renal glycosuria in man is a rare condition, the genuineness of which is now strongly probable. Naunyn has long recognized it, though under a rather lax definition. Von Noorden [(3), p. 529 and (1), p. 37] has considered it not demonstrated. The question is an involved one, because mild cases of diabetes may show very slight hyperglycemia, Bright's disease is sometimes accompanied by hyperglycemia, and complications and transitions of diabetes and nephritis are known to occur.

Renal glycosuria means glycosuria with normal glycemia, relatively independent of diet. In other words, the excretion of sugar must be due to abnormal permeability of the kidney, while the tissues still retain the normal power of utilizing dextrose.

The name diabetes is unjustifiable. Diabetic symptoms are absent, but those of nephritis, neurasthenia, and malnutrition are frequent. Almost always the glycosuria is very slight, a mere fraction of one per cent. Cases of intense glycosuria have never been demonstrated as renal. Wadsworth described a man who at the age of 25 accidentally discovered his urine to be heavy with sugar. He was thereafter under observation for six years. His urine all the time had a specific gravity of about 1040, and contained about 10 per cent glucose, the amount of sugar excreted

being about 32 ounces each 24 hours. The glycosuria was diminished by carbohydrate-free diet or by milk diet, but sugar-freedom was never obtained. The general health was excellent, and there were no other signs or symptoms of diabetes. The investigation was then extended to the patient's family. He was the eldest of eleven children, all living and apparently in perfect health; but examination showed slight or heavy glycosuria in every one. The father and mother were healthy and had normal urine. The father later died of grippe at the age of 54. The entire family history was negative, the ancestors on both sides having lived healthy and often unusually long lives. The important features of this case are the long period of observation and the family peculiarity. The greatest lack is of blood-sugar determinations. In their absence, hyperglycemia may be supposed; hence the cases would not be renal glycosuria. While most exceptional and remarkable, and perhaps representing some unknown derangement of metabolism, the cases might still possibly be interpreted as atypical diabetes mellitus. Nothing hinders the diagnosis except the unusually long duration without symptoms other than glycosuria; but there are cases, as that of Forsell mentioned by Kleen, in which patients have retained fair health for as long as twenty years, while on unsuitable diet and excreting enormous quantities of sugar.

Another atypical case is that of Kolisch and Buber. The patient was a girl of 25, in good health, with glycosuria of 5–8–10 per cent, the excretion running as high as 80 g. in 24 hours. With glycosuria of 5 per cent, the blood-sugar was 0.14 per cent. Thirst and polyuria present at the beginning soon disappeared. Nitrogen excretion was normal; there was no acetone. Nutrition was excellent. Fasting promptly abolished the glycosuria, but it returned not only on carbohydrate but also on other diet. Observation was for six months, during which the condition remained unchanged. This again is a very atypical case, not renal glycosuria, probably diabetes. The figure of 0.14 per cent represents hyperglycemia; the excretion was remarkably high, but von Noorden has recognized such possibilities in early diabetes. The peculiarities as respects diet might hypothetically be explained on the supposition that the patient was one of those in whom meat readily causes glycosuria. The authors properly termed the case diabetes decipiens.

Naunyn (pp. 132–135) presents several cases of suspected

renal glycosuria, but most of them seem to be nothing but mild or masked diabetes. The most convincing is Case 40, with the table on page 134 showing a maximum glycosuria of only 0.9 per cent, which after 30 g. sugar by mouth actually fell to 0.5 per cent. Cases of renal hemorrhage with sugar excretion are classed by Naunyn under renal glycosuria, but they may perhaps be nervous, the glycosuria resulting from stimulation of sensory nerves in renal colic, etc. The glycosuria of chyluria, classified here by Naunyn, may perhaps be of renal origin, but may also be of nervous or some other cause; the condition is not understood.

Klemperer (1, also *2A*) reported a case of old nephritis, in which 0.35 per cent glucose was found in the urine, and 0.18 per cent in the blood. The unusual feature was that bread diet, and dextrose up to 150 g., are said to have caused no increase of sugar either in urine or in blood.

Lüthje (*1A*) reported a case of slight glycosuria, very little influenced by food, and with blood-sugar of 0.055 per cent. Von Noorden [(3); p. 531] casts doubt upon this blood-analysis. If it be rejected, the case is explainable as a simple, very mild diabetes.

Bönniger reported a convincing case. The patient was a chronic alcoholic, aged 37, who entered the hospital to sober up. At an insurance examination in 1905, 2 per cent sugar had been found in his urine. On entrance into the hospital, his urine contained casts and a little albumin, but these quickly disappeared. Sugar was absent at entrance, but later 2 per cent was found. The sugar diminished to 0.2 per cent on ordinary diet, and the strictest anti-diabetic régime could not bring it below this figure. Doses of 100 g. dextrose, given with abundant bread, potatoes, and rice, had not the slightest effect upon the sugar of urine or blood. In different specimens during the day, sugar excretion was found to be independent of meals. Diuretics and muscular labor had no effect upon the glycosuria. The glycemia was never above 0.097 per cent, and one analysis showed it to be 0.062 per cent at a time when the urine contained 0.5 per cent. Bönniger's positive conclusion concerning this case seems justified.

Siebke reported a case not so fully studied. The patient had tuberculosis of the kidneys, and exereted 0.1–0.2 per cent sugar in the urine, irrespective of diet, and with no change when 50 g. dextrose was fed fasting. Even in the absence of blood analyses, the diagnosis of renal glycosuria seems probable in this case.

Weiland (3) reported three cases. The first is of a healthy man who entered the hospital only for an attack of pain in the appendix region. Sugar was found in his urine, varying under different conditions from 0.1 per cent to 2.3 per cent. Albuminuria and all other pathological conditions were absent. The period of observation was somewhat less than 3 months, and during this time many dietetic tests and 6 blood-analyses were made. The blood-sugar was always below 0.1 per cent, and once was only 0.054 per cent. The sugar-excretion was remarkably independent of carbohydrate and even of sugar in the diet. Nevertheless, strict diet did occasionally succeed in reducing the glycosuria to practically nil, and on some occasions a rich carbohydrate diet did result in marked glycosuria (for example, 2.3 per cent after bread and 50 g. dextrose). This period establishes a strong probability of diabetes, for it is significant that the glycosuria rose when sugar was kept up day after day. Weiland's second case is of a healthy man who began to feel weak, and lost 30 pounds of weight in 4 months. In a hospital, sugar was found in his urine, but after 4 weeks of dieting he was discharged sugar-free on strict diet plus 1 litre of milk daily. Weakness continued. The record then shows that the tolerance for carbohydrate food in repeated tests was high. There were no tests with dextrose. The glycosuria on mixed diet did not go above 0.38 per cent, and on strict diet it could be reduced to traces or nothing. The blood-sugar varied from 0.071 to 0.101. Acetone and β-oxybutyric acid were present even when the diet included carbohydrate. Two years from the time sugar was first found, the patient was not only no worse, but had attained subjective well-being. The case might still have been an atypical diabetes. Weiland's third patient was a neurasthenic aged 23, glycosuric for 2 years. Occasionally traces of albumin and red corpuscles were found in his urine. When 300 g. bread was given, his glycosuria rose to 1.85 per cent; on strict diet it went down to zero or traces; on still heavier carbohydrate food it rose to 2.5 per cent; on strict diet it returned to zero or traces. There were no dextrose assimilation tests. The blood-sugar analyzed once was 0.079 per cent. The case was apparently an atypical mild diabetes.

Garrod (3) has published the case of a woman with glycosuria of 0.27 to 1.086 per cent, becoming no worse during two years of observation. Strict diet, or bread up to 180 g., made no difference. There was no blood examination, and the one feeding of

dextrose amounted to only 10 g. A conclusion concerning the case is therefore impossible.

Tachau (2) has published the most recent report. A man 21 years old entered the hospital on account of abdominal pain and diarrhea. He appeared poorly nourished, and the urine contained a little albumin. This disappeared within a few days, and the patient soon recovered well-being. The sugar-excretion, in fractions of one per cent, amounted to 6 g. in 24 hours at the outset, but diminished even on mixed diet, and disappeared on strict diet, returning in traces when mixed diet was resumed. Doses of 100 g. dextrose were without effect. The blood-sugar was carefully followed by analyses both before and after the test-doses of sugar, and the uniform absence of hyperglycemia was demonstrated. Tachau's case therefore stands as a positive example of renal glycosuria.

2 C II. Glycosuria Due to Breaking Up of Abnormal Compounds.

Phloridzin glycosuria will be considered in Chapter XV. The mellituria caused by injections of glycogen, dextrin, starch, and cane-sugar has been described in Chapter II.

D. Nervous System.

I. Central.

(*a*) *Piqûre, etc.* (*b*) *Emotions.*

The subjects of the piqûre and analogous nervous lesions, and also of emotional glycosuria, will be reserved to Chapter XVII.

(*c*) *Asphyxia.*

In a series of researches by pupils of Hoppe-Seyle — Araki (1 to 4), Irisawa, Zillesen — it was proved that simple asphyxia, and a long list of conditions associated with deficiency of oxygen-supply to the tissues, cause excretion in the urine of both glucose and lactic acid, the latter being looked upon as a product of imperfect combustion. The glycosuria caused by asphyxia and all asphyxial agents is of central origin. It is dependent upon the glycogen-supply of the liver. Though it can be produced when all nerves to the liver are cut [Macleod (3)], it cannot be produced

when the splanchnic nerves of both sides are cut. Wertheimer and Battez (3), from experiments with atropin, came to the conclusion that direct secretory nerves to the liver have no share in asphyxial glycosuria. The following is an alphabetical list of chemical agents which regularly or occasionally cause glycosuria, of which the mechanism is certainly or possibly asphyxia.

Acetone.
Acids (hydrochloric, hydrocyanic, lactic, oxalic, salicylic, sulphuric, lower fatty acids).
Alcohol.
Amyl nitrite.
Anilin.
Arsenic.
Atropin.
Barium chloride.
Carbon dioxide.
Carbon monoxide.
Chloral.
Chloralamid.
Chloralose.
Chlorates.
Chloroform.
Coal-tar products.
Cocain.
Coniin.
Copaiba.
Curare.
Cyanides.
Digitalis.
Ether.
Hydrogen.
Hydrogen disulphide.
Methyl delphinin.
Morphin (opium).
Nicotin.
Nitrobenzol.
Nitrotoluol.
Nitrous oxide.
Orthonitrophenyl-propionic acid.
Oxalates (sodium and ammonium).
Paraldehyd.
Phenol.
Phosphorus.
Pilocarpin.
Piperidin.
Pyrogallol.
Salicylates.
Salts of magnesium (intravenously).
Secale cornutum.
Strychnin.
Sulphonal.
Turpentine? (probably not glucose in urine).
Urethane (contributes toward if does not cause glycosuria).
Veratrin.
Veronal.

Naunyn (p. 53) calls attention to the fact that asphyxia seems never to cause glycosuria in human patients, in whom there may be serious and prolonged deficiency of oxygen owing to asthma, pneumonia, or pulmonary œdema. Hoeniger has contributed a paper on the transitory glycosuria of new-born infants after diffi-

cult deliveries; but the glycosuria occurs particularly when the delivery was instrumental, and nerve-stimulation may play a part as well as asphyxia. Macleod (1) classifies the glycosuria following vagus stimulation as asphyxial, and asserts that glycosuria remains absent when asphyxia is guarded against.

No attempt will be made to go into the earlier history of researches concerning the effects of any of the above drugs. This subject will be found sufficiently covered in the texts of Naunyn, von Noorden, Lepine, and Kleen. In this place, only some of the later or special investigations will be noted concerning asphyxial agents.

Acetone and acids are reserved to Chapter XIV.

Alcohol seldom causes glycosuria, but in large quantity increases considerably the tendency to alimentary glycosuria. Alcoholism and delirium tremens are among the conditions in which non-diabetic glycosuria *ex amylo* is occasionally found. Alcohol is classed with the anæsthetics; there is no specific effect.

Amyl nitrite was studied especially by Araki (2). Earlier references are given by Lepine [(1), p. 314].

Anilin is mentioned by Pollak (2).

Arsenic and the writers who have witnessed the (rare) glycosuria from it are mentioned by Kleen (p. 53).

Atropin glycosuria is described by Lepine [(1), p. 314]. The experiments of Wertheimer and Battez (3) show that the sugar excretion is slight — after 5 to 10 centigrams of atropin intravenously in rabbits, glycosuria of 0.1 to 0.7 per cent, and negative results not infrequent.

Barium chloride glycosuria is described in rabbits by Neubauer (4).

Carbon dioxide may at first be thought of as a merely passive agent, in excluding oxygen. But Edie [see also Edie, Moore and Roaf] has published experiments to show that the glycosuria resulting from partial asphyxia is due not to lack of oxygen but to excess of CO_2. The presence of 10–15 per cent CO_2 causes glycosuria, even if the oxygen present be more than that in atmospheric air. A low percentage of oxygen without CO_2 causes no glycosuria. The high CO_2 percentage necessary for glycosuria also causes, in dogs and cats, anæsthesia. Accordingly, CO_2 merely follows the general law that anæsthetics produce glycosuria. On the basis of Edie's work, the active influence of high percentages of CO_2 in causing glycosuria must be accepted, but

the belief in deficiency of oxygen as a glycosuric agent has not been given up. The opposite side of the picture is presented by the authors who have worked with acapnia, or deficiency of CO_2. The influence of such deficiency in shock and various other conditions has been emphasized of late, and Henderson and Underhill have brought it into relation with glycosuria. They have studied acapnia in peptone glycosuria, emotional glycosuria, piqûre, experimental diabetes, piperidin glycosuria, and the glycosuria following laparotomy and excessive artificial respiration. They conclude that acapnia is the etiologic agent or a concomitant factor in many types of glycosuria.

Carbon monoxide glycosuria has been the object of considerable research. The discovery by Richardson and the early general observations are described in texts. Its status as an asphyxial glycosuria was established by Araki (1). The glycosuria may be considerable; Senff found 1.5 to 4 per cent; but the duration is only a few hours. Straub (1) made the surprising observation that CO glycosuria is best obtained with meat feeding. Heavy carbohydrate feeding with albumin hunger prevents the glycosuria; especially, after pure carbohydrate feeding CO produces no glycosuria. Rosenstein continued and confirmed the observations of Straub. Vamossy came to the same conclusions. Nevertheless, the sugar in CO glycosuria is derived from the glycogen of the liver, just as in most other cases, and in absence of liver-glycogen there is no excretion of sugar. Starkenstein (3) has made one of the latest and fullest contributions to this subject. He classifies CO glycosuria as of typical asphyxial type, and conclusively demonstrates the central mechanism. An action upon the adrenals, just as in the case of piqûre, was proved by tests of the adrenals for adrenalin, and by microscopic examination. Physiologically and anatomically, the adrenals were shown to be exhausted after CO-poisoning. His experiments tend to show that chloral is a direct antagonist of adrenalin. There is considerable theoretical interest in his observation that chloral prevents piqûre glycosuria, but does not prevent CO glycosuria in dogs; an additional obstacle is thus interposed to interpreting both these forms as simple adrenalin glycosuria. Starkenstein's experiments fully support his positive conclusion concerning the central mechanism in CO glycosuria, but his single negative result after cutting the splanchnics does not necessarily rule out all peripheral effect. It is conceivable that in extreme cases there

may also be some peripheral effect, upon the liver-cells or upon the peripheral nervous mechanism. This seems to be likewise the view of von Noorden [(1), p. 27]. Kahn (5) has lately published similar studies of CO poisoning in monkeys.

Chloral, chloralamid, chloralose, and chloroform rank with the other anæsthetics. Pavy and Godden (1) state that chloroform glycosuria can be prevented by intravenous injections of sodium carbonate. After chloral, it is necessary to guard against errors due to the presence of urochloralic acid (one of the group of combined glycuronic acids, reducing copper but not fermenting) in the urine.

Chlorates rank with the other blood-poisons.

Coal-tar drugs are mentioned casually as rare causes of glycosuria.

Cocain may belong properly in this group or among the nerve-poisons. It was one of the drugs used by Araki (2).

Coniin was used in experiments by Underhill (1).

Copaiba glycosuria is mentioned by Garrod (1).

Curare glycosuria was discovered by Claude Bernard. Naunyn (p. 51) and Lepine [(1), p. 317] cite various authors who showed that this glycosuria is prevented by adequate artificial respiration. Penzoldt and Fleischer first called attention to the asphyxial factor. An experimental support of this view, and a review of the literature, will be found in the paper of Sauer. But Lepine is perhaps correct in concluding that asphyxia is not the sole cause of curare glycosuria. Winogradoff claimed that frogs do not show curare glycosuria after removal of the liver. Considerably later, Langendorff (2) reported the opposite, viz., that curare produces glycosuria in frogs after removal of the liver. The question cannot be called settled, but season and other factors may explain some differences, and in general positive results are here worth more than negative. Curare glycosuria in frogs therefore has some claim to rank as a "muscle" as well as a "liver" glycosuria. Morishima confirms this view by finding that curare glycosuria is an inconstant phenomenon in both frogs and rabbits. In frogs, the glycosuria bears no fixed relation to the glycogen-content of either liver or muscles. Araki investigated curare among other asphyxial agents, and claimed the glycosuria to stand in relation with liver-glycogen. Macleod (3) proved that after establishing an Eck fistula and ligating the hepatic artery, curare and mechanical asphyxia alike fail to cause glycosuria in dogs.

His results are sufficiently conclusive for dogs, but do not necessarily affect the findings in frogs.

Cyanides cause glycosuria supposedly through their toxic inhibition of oxidation.

Klemperer (ref. by Kleen, p. 58) is said to have reported a case of digitalis glycosuria.

Glycosuria from ether is occasionally seen after operations. Naunyn (p. 52) quotes Frerichs as having found that large inhalations of ether without narcosis fail to cause glycosuria. According to the extensive series studied by Pflüger (5), with Schöndorff and Wenzel, and by Pflüger (11), surgical anæsthesia must be considered only rarely a cause of glycosuria. Seelig reported that ether anæsthesia produces more or less glycosuria in meat-fed dogs, whereas preliminary feeding with carbohydrate prevents the glycosuria. The glycosuria is demonstrable during the anæsthesia, but disappears promptly thereafter. Hyperglycemia accompanies. The glycogen of the liver is much reduced. Intravenous injection of oxygen prevents glycosuria, but does not stop an existing glycosuria. Swan recently has observed that certain human postoperative urines turn almost black on standing, give typical Fehling and Boetger tests, but fail to ferment or form typical osazone crystals. Hawk (2) has made a recent contribution to this subject. Also recently, King, Chaffee, Anderson and Redelings have concluded that ether glycosuria is the result of a direct action upon the liver. This conclusion is supported by experiments with Eck fistulas, section of nerves, etc. King, Moyle and Haupt have produced glycosuria by intravenous injections of ether without asphyxia. The part frequently played by asphyxia however need not be denied.

Hydrogen inhalation presumably acts by exclusion of oxygen.

Hydrogen disulphide is one of the blood-poisons.

Methyl delphinin is analogous to curare.

Morphin glycosuria is treated by Lepine [(1), pp. 311 ff] somewhat more fully than by most authors. In acute poisoning, the glycosuria is generally of only a few hours' duration, is accompanied by hyperglycemia, also by polyuria followed by anuria, depends upon liver-glycogen, and is prevented by section of the splanchnics. Eckhard found that glycerin prevents morphine glycosuria (just as after piqûre), and Luchsinger partially confirmed the statement. In cases of chronic poisoning or opium habit, glycosuria is slight and rare. Two points require special notice

concerning morphine (or opium). The first is that the reducing substance in the urine is not always dextrose. Jastrowitz and Salkowski proved the alternation of dextrose and a pentose in the urine. Spitta denied that glycosuria occurs after morphine, and concluded that the reducing substance is probably an unknown acid, closely related to levulose. The second point concerns exceptions to the law of summation of effects of glycosuric agents. Opium, chloral, ether, and chloroform are able to prevent the glycosuria from piqûre and similar agents; less powerful anæsthetics may fail to do so. Schlesinger (1) found that opium may sometimes prevent alimentary glycosuria. His explanation that it delays absorption of the sugar is under dispute. The empiric use of opium in diabetes is well known. It probably acts by diminishing nervous excitability in the splanchnic domain.

Nicotin glycosuria was first observed by Lepine [(1), p. 303]. Cannon, Aub and Binger have lately shown that nicotin increases adrenal secretion. The drug has been used less for producing glycosuria than for determining the point of attack of glycosuric agents, such as adrenalin. The researches of Hirayama and of Starkenstein (3) will be mentioned in the chapter on adrenalin.

Nitrobenzol, nitrotoluol, orthonitrophenyl-propionic acid, and phenol may rank among the blood-poisons. Glycosuria has been observed in phenol poisoning; and Borchardt (2) mentions that doses of $\frac{1}{2}$ cc. carbolic acid subcutaneously in rabbits may cause glycosuria.

Oxalates (sodium and ammonium) may produce slight glycosuria. Rosenberger (p. 105) refers to the literature. The mechanism is not certain.

Nitrous oxide and paraldehyde follow the rule of anæsthetics.

Glycosuria from phosphorus poisoning is mentioned by Lepine (p. 320) and by Kleen (p. 53). A disturbance of oxidation may be supposed to constitute part of the mechanism.

Pilocarpin glycosuria was observed by Doyon, Kareff and Fenestrier [C. r. soc. biol., 1904, p. 1; ref. by Underhill (1)].

Piperidin glycosuria was established as asphyxial by Underhill (1).

Pyrogallol ranks among the blood-poisons. The glycosuria was observed by Herter [ref. by Underhill (1)].

Glycosuria from salicylates is mentioned by Kleen (p. 53) and by Underhill (1).

Underhill and Closson (1), following up observations of Meltzer and Auer, found hyperglycemia and glycosuria produced by intravenous injections of magnesium sulphate.

Glycosuria from Secale cornutum was witnessed by von Noorden.

The early observers of strychnin glycosuria are cited by Naunyn (p. 51). Lepine states that it is unknown in man. It has also not been found in rabbits. Frogs have been the animals used for study, and in them the glycosuria begins after about 24 hours, and may last as long as 5 days. It is not dependent on tetanus. Langendorff showed that it depends upon the presence of the liver, and even varies according to the size of the liver. Glycogen is quickly consumed, irrespective of glycosuria; and, as is well known, strychnin is one of the favorite agents for rendering animals glycogen-free. The experiments of Araki (1) placed strychnin glycosuria in the asphyxial list.

Sulphonal ranks with the hypnotics.

Turpentine is placed in this list doubtfully. Lepine [(1), p. 321] discusses it briefly. Though the sugar in the urine is fermentable, it appears not to be dextrose; therefore we cannot place this among the renal glycosurias, as the natural tendency would be. Neither is there any evidence that the mechanism is asphyxial.

Urethane was used by Ritzmann as an anæsthetic not causing glycosuria. But Underhill (4) found that it contributes toward the occurrence of adrenalin glycosuria.

Veratrin is mentioned as a cause of glycosuria by Underhill (1) and by Kleen (p. 58), and was one of the agents employed by Araki.

Veronal is analogous to sulphonal.

(*d*) *Nerve-Poisons.*

The list of nerve-poisons causing glycosuria by central stimulation is largely uncertain. A few have been positively demonstrated, and the possibility of others is thus established. A series including positive and doubtful members may be suggested as follows:

Caffein.
Diuretin (theobromin).
Strychnin.
Albumoses and peptones.
Morphin?
Cocain?
Organ extracts and sera?
Fecal extracts, etc.?
Tuberculin and toxins?

Caffein and diuretin are fully established as agents which cause glycosuria by a central stimulation analogous to piqûre. As previously mentioned, Jacobi looked upon them as causes of pure renal glycosuria, but Richter and Rose proved that hyperglycemia is present. Richter (2) proved that the glycosuria is dependent upon liver-glycogen, and Pollak (2) that glycosuria remains absent after splanchnicotomy. Nishi (1*A*) studied carefully the mechanism in case of diuretin. He showed experimentally that diuretin hyperglycemia remains absent after

(*a*) Cutting both splanchnics.

(*b*) Cutting merely the left splanchnic.

(*c*) Removing both adrenals.

(*d*) Extirpation of right adrenal and cutting all nerves to left adrenal.

(*e*) Complete enervation of both adrenals.

On the other hand, diuretin glycosuria persists after

(*a*) Cutting the right splanchnic nerve.

(*b*) Extirpation of one adrenal (either right or left).

(*c*) Cutting all adrenal nerves except those from the right cœliac ganglion to the right adrenal.

Nishi therefore came to the following conclusions:

1. The stimulus from the sugar-centre goes not to the liver but to the adrenals.

2. The stimulus goes to both adrenals by the left splanchnic nerve.

As will be mentioned in connection with piqûre and the adrenals, Nishi's finding of innervation of both adrenals entirely by the left splanchnic is contrary to the results of others, especially Kahn (2). Also, the belief that nervous stimuli affect only the adrenals and not other abdominal viscera is probably incorrect.

Miculicich has found that hirudin inhibits adrenalin but not diuretin glycosuria. Ergotoxin inhibits both.

Starkenstein (3) made the observation that when caffein is given first, then adrenalin injected 1½ hours later, the result is not a summation of glycosuric effects, but rather the opposite, supposedly because the caffein has tired the nervous mechanism.

Strychnin is generally classed among the agents that cause glycosuria solely through asphyxia; *e.g.*, Starkenstein (3) thus classifies it. The question is difficult to decide, for strychnin

glycosuria is feeble and uncertain at best. Strychnin acts so preëminently upon the nervous system, that a direct nervous action as a factor in strychnin glycosuria is a natural assumption. One piece of evidence speaks for this view. Strychnin glycosuria in the frog is said to require 24 hours to appear, and then to continue sometimes for 5 days. This is not the behavior of asphyxia.

The same reasoning as for strychnin applies also to morphin, cocain, and other drugs.

The renal poisons frequently produce hyperglycemia. There is a mere possibility that this may be of central nervous origin.

Albumoses and peptones as glycosuric agents were discovered by Henderson and Underhill. According to these authors, the effect is due to acapnia. At any rate, asphyxia seems to be ruled out, and a central nervous mechanism must be concerned. They therefore belong positively in this group.

Under 2 B III, reference was made to the glycosuric effects of organ extracts, foreign sera, etc. A central nervous origin of the hyperglycemia is at least possible.

The toxic glycosuria resulting from injections of fecal extracts has caused a little confusion in the past, and is still heard of occasionally. De Dominicis [ref. by von Noorden (3), p. 625, and by Biedl (3), p. 385] and later Töpfer [ref. by von Noorden, l.c.] performed such experiments in connection with the etiology of diabetes. The claim is that feces or duodenal secretion of diabetic persons or dogs cause greater glycosuria than the normal products. Others have made similar claims for injections of diabetic urine. Von Noorden thinks fresh researches might profitably be undertaken; and Senator (1) paid serious attention to these supposedly "suggestive" experiments in connection with the possible infectious origin of diabetes. The glycosurias in question are obviously toxic, without bearing upon diabetes. It would not be surprising if the mechanism were at least partly nervous.

Teschemacher [Dtsch. med. Wchnschr., 1895, p. 277. Ref. by Lepine] reported one case of glycosuria after injection of Koch's tuberculin. Since glycosuria occurs in a variety of infections, it might follow the injection of various toxins. And since the general reaction is largely a central nervous phenomenon, the glycosuria may have a similar origin.

The slight glycosuria rarely associated with cysticerci and intestinal worms [Lepine (1), pp. 330–331] may perhaps be one expression of toxic excitation of the nervous system. See also D I (i).

(*e*) *Salt Injections.*

Salts as glycosuric agents clearly belong in the list of poisons of the central nervous system; but so much work has been bestowed upon salt-glycosuria that a separate status for it is convenient. The German name of "Durchspülungsglykosurie" gives wrong impressions of a mere "washing out" of sugar, and should be abandoned, for the effect is admittedly nervous. Bock and Hoffmann are credited by texts with the discovery that intravenous injection of 1 per cent NaCl solution in rabbits causes a slight glycosuria. In their experiments polyuria preceded glycosuria. The injection was proved to cause hyperglycemia, and to exhaust the glycogen of the liver. Külz and others [ref. in texts] added to the list of salts, so that we now know that glycosuria can be caused by sodium acetate, bicarbonate, phosphate, succinate, sulphate, and valerianate. Külz also proved that cutting the splanchnic nerves prevents salt-glycosuria; *i.e.*, the origin is central.

Fischer (1 and 2) carried out the most extensive research concerning salt glycosuria. He found that intravenous injection of NaCl, in M/6 solution or stronger, causes glycosuria in rabbits after a certain latent period. Weaker solutions cause only a delayed, faint glycosuria, or none. Addition of $CaCl_2$ to the NaCl solution prevents glycosuria, or stops it after it has begun, and glycosuria returns when injection of pure NaCl solution is resumed. The results were shown to be similar for various other salts. Non-electrolytes such as urea, glycerin, and alcohol failed to cause glycosuria, hence the effect is concluded to be not osmotic, but a specific action of the salt. This action is shown to be exerted upon the medulla. Especially, injection of the solution into the central end of the axillary artery (sending it directly to the brain) was found to cause quicker and greater glycosuria than the ordinary intravenous injection.

Underhill and Closson (1) laid stress upon the effects of dyspnea and of altered renal permeability as factors in salt glycosuria.

McGuigan and Brooks ruled out increased ferment activity, and disputed the rôle of renal permeability, as factors in salt glycosuria.

Burnett demonstrated the inhibiting effect of potassium salts upon the glycosuria produced by sodium salts. This and other

work on this subject has been dominated by the ionic hypotheses of Loeb.

Watermann and Smit claimed that the adrenalin of the blood is increased in salt glycosuria. While it may be believed that the adrenals under these conditions are excited to increased activity, it is improbable that an increase of adrenalin in the blood can be demonstrated.

McGuigan (2) found that removal of both adrenals in rabbits renders salt glycosuria impossible, while phloridzin glycosuria occurs readily. Removal of the adrenals in dogs makes salt glycosuria more difficult, but it can be produced. In cats, epinephrectomy seems to be without influence upon salt glycosuria. Such experiments destroy the idea that salt glycosuria is purely an adrenal glycosuria.

Freund drew a parallel between the curves of temperature and of glycosuria caused by salt and by adrenalin, and inferred that the agency was the same in both cases.

Pavy and Godden (2) showed that salt solution reduces the tolerance of rabbits for intravenously injected dextrose.

Verzar (1) studied the changes in the respiratory quotient produced by intravenous injections of NaCl solution.

Wilenko (3) came to the following conclusions. (1) Intravenous injection of concentrated (20 per cent) salt solution produces, by stimulation of the central nervous system, a hyperglycemia in which the muscles and probably also the liver lose glycogen. (2) The nervous stimulus is a kation effect. (3) Intravenous injection of concentrated salt solutions changes the permeability of the kidney for sugar. The change is produced by osmotic factors, and consists apparently of two phases, first an increased and then a decreased permeability of the kidney for sugar.

(*f*) *Irritation of Afferent Nerves.*

Glycosuria from stimulation of sensory nerves has long been known. The following examples are taken from the literature reviewed by Pflüger [(1), pp. 395 ff]. But afferent is a better word than sensory in this connection, for we are not sure that all the afferent stimuli concerned are sensory. The following writers are quoted as having discovered that glycosuria can be caused by the following means:

Cyon and Aladoff. — Extirpation of inferior cervical ganglion, of 1st and 2nd thoracic ganglia, and cutting annulus Vieussenii.

Filehne. — Stimulation of central end of depressor nerve. Confirmed by Laffont, Külz, Eckhard.

Külz. — Cutting of sympathetic in neck and electrical stimulation of central end. Cutting and electrical stimulation of sciatic.

Schiff. — Cutting of either right or left sciatic nerve.

Böhm and Hoffmann. — Cutting of sciatic nerve.

Ryndsjun. — Drawing a thread soaked with croton oil through the sciatic nerve.

Froning. — Cutting out a piece of sciatic nerve, and stimulating the nerve with permanent ligature, phenol, potassium bichromate, or Fowler's solution. Glycosuria thus produced in dogs, cats, and rabbits sometimes lasted several days.

Among reflex glycosurias must probably be included the form discovered by Eckhard and by Cyon and Aladoff, produced by operations upon the cervical and upper thoracic sympathetic. More or less glycosuria was found to follow cutting the ganglia at this level, especially the inferior cervical ganglion. Simultaneous section of the eighth cervical and first thoracic pairs of nerves frequently causes glycosuria. The extirpation of the inferior cervical ganglion, or cutting all its nervous connections, or the simple section of its two branches which form the *annulus Vieussenii*, produces glycosuria comparable to that following piqûre. All these forms of glycosuria are prevented by section of the splanchnics. Since the efferent tracts for sugar-regulation do not traverse the above-mentioned sympathetic trunks or ganglia, it must be presumed that they contain afferent fibres, whose injury produces reflex effects transmitted through the splanchnics.

Many glycosurias in the literature, to some of which great importance has sometimes been attached, may be interpreted as simple effects of stimulation of afferent nerves. Among these is the glycosuria observed by de Renzi and Reale after extirpation of the salivary glands, which it was necessary for Minkowski [(1), p. 56] to prove to be not diabetes. In this same list belongs the "duodenal diabetes" reported by several authors. Afferent-nerve stimulation may explain the glycosuria following some surgical operations (aside from the anæsthetic), and it may partly explain the glycosuria of new-born children after difficult labors (aside from asphyxia. *Cold* is also sometimes perhaps an additional factor). Pflüger (5 and 11) showed that operations comparatively rarely cause glycosuria, except in case of nervous injury. Rose,

also Nishi (1*A*), proved that even in so sensitive an animal as the rabbit, abdominal operations and cutting of certain nerves can be performed without causing hyperglycemia.

Bang, Ljungdahl and Böhm claimed (probably incorrectly) that stimulation of the central end of the cut vagus increases the diastase of the liver at the end of an hour; but hyperglycemia and glycosuria are present before this time; and they conclude that glycosuria produced through the splanchnics and through the vagus is different, and that the latter is a "muscle glycosuria." Against this claim may be set Macleod's demonstration that cutting the splanchnic nerves prevents glycosuria from vagus stimulation.

Cavazzani and Finzi found that the liver diastase is unchanged by vagus stimulation, but the sugar in the blood of the hepatic veins is increased.

Cannon and Hoskins reported that electrical stimulation of the sciatic nerve is followed by an increase of adrenalin in the blood.

Macleod (1) found that stimulation of the central ends of the cut vagi in the neck causes hyperglycemia when no precautions are taken against asphyxia, but not when asphyxia is prevented. Stimulation of the spinal cord at any level fails to cause hyperglycemia when asphyxia is prevented. He concludes that there is no evidence that stimulation of the central end of the vagus can reflexly produce hyperglycemia. This conclusion may be justified in a strict sense, but it should not be construed as an absolute proof that vagus irritation cannot cause glycosuria reflexly, nor should it militate against the general view that stimulation of afferent nerves per se may cause glycosuria. The above-mentioned experiments of Froning, showing that sciatic stimulation may give rise to glycosuria lasting several days, are sufficient to indicate that something more than asphyxia is here concerned. Similar experiments might prove successful for the vagus. Important in this connection is the observation of Starkenstein (3) that vagus stimulation causes hyperglycemia even after epinephrectomy.

Pflüger [(1), p. 401] states that glycosuria frequently accompanies sciatica; and he refers to case-reports by Braun, Eulenburg and Guttmann, and Erb. Lepine [(1), pp. 254 ff] adds an additional case by Hallerworden, and refers to other reports of transient glycosuria following fracture of limbs.

Glycosuria in attacks of gall-stone colic is mentioned by all authors. It is uncommon, and receives notice largely on account

of the superstitions that have clung about the liver. In some cases it may perhaps be due partly or wholly to sudden poisoning of the liver with bile, but there is no reason why the intensely painful nervous effects should not be considered a principal factor. Of a different order are those cases in which the pancreas is affected, probably by bile stasis or inflammatory involvement. Garrod (2) mentions a glycosuria of 7 per cent cured by removal of gallstones. Here a true diabetic element is to be thought of.

Irritation of peripheral nerves is claimed to be in rare cases a factor in the production of diabetes. The literature on this point will be reviewed in Chapter XVII.

(g) *Cold.*

Glycosuria due to cold might be classified under the above heading of stimulation of afferent nerves, but is sufficiently distinctive to deserve separate treatment.

Böhm and Hoffmann (2 and 3) discovered that when cats were under-cooled in not too extreme degree, a transient glycosuria resulted. Several hours before death from cold, the glycosuria stopped, and considerable sugar-free urine was secreted, even though hyperglycemia persisted. At death, all carbohydrate was found absent from the bodies of such animals. But if the cooling was too extreme or too rapid, glycosuria failed to occur, and carbohydrate was found in the bodies at death, presumably because the temperature was too low for its utilization.

Araki (3) produced glycosuria in rabbits by packing them in snow. He explained the phenomenon, as usual, as a deficiency of oxidation.

Mention has already been made of the experiments of Lüthje and others, proving that incompletely depancreatized diabetic dogs excrete more sugar at lower than at higher temperatures, and that normal dogs show hyperglycemia from cold. A prevalent explanation is that in the cold an animal needs more sugar for combustion purposes, hence increased transportation occurs through the blood. Von Noorden [(1), p. 108] evidently still holds to this belief.

Pflüger (13) believed that he had produced diabetes by extirpation of the duodenum in frogs; but the glycosuria observed was due to the fact that they were kept on ice.

Loewit (1 and 2) made a careful study of cold-glycosuria in frogs. The sugar excretion is frequently very marked, but there

are sometimes negative results which are difficult to explain. Neither the glycogen-richness nor the degree of hyperglycemia is necessarily the determining factor. Albuminuria occurs in every case. There is no increase of adrenalin in the blood, hence increased activity of the chromaffin system is not the cause. After as complete as possible extirpation of the liver, cold-glycosuria is still obtained. A "muscle-glycosuria" therefore exists here. Loewit makes the interesting point that since the frog is a cold-blooded animal, the increased sugar of the blood cannot be due to need of an increased supply to keep up the body-temperature.

It is not necessary to suppose that the need of the muscles for sugar (in mammals) may not, in this as in other cases, have an influence somehow in producing increased sugar-formation in the liver. But in view of the above experiments, the essential cause of cold-glycosuria cannot be found in a "call" of the muscles for sugar. The true explanation may be that of Pflüger, viz., that the glycosuria is due to a powerful reflex effect of the cooling of the skin upon the central nervous system; or it may be imagined that the under-cooled blood itself acts as a direct stimulus to the nervous system. Two facts support this view; (*a*) the occurrence of glycosuria in a cold-blooded animal; (*b*) its occurrence after removal of the liver, showing that the muscles themselves pour an excess of sugar into the blood.

Cold-glycosuria is not often seen clinically. But Bamberger, and later Glaessner [ref. by Lepine (1), p. 328], reported cases of transient glycosuria in persons who had attempted suicide by drowning, which undoubtedly belong in this category. Similar cases, followed even by diabetes, are reviewed by Rosenberger.

(*h*) *Fever.*

The increase of blood-sugar caused by elevation of temperature, due to artificial heat, brain-puncture, or infection, has been discussed in Chapter I. A central nervous mechanism may probably be assumed. Strictly speaking, febrile glycosuria is non-existent. Traces of glycosuria occur in a variety of febrile diseases; and in most such diseases, alimentary glycosuria (*e saccharo*, sometimes *ex amylo*) is easily produced. But as Hollinger and others observed clinically, and Lepine and Boulud (7) proved experimentally, hyperglycemia under these conditions depends upon intoxication rather than upon temperature. Elevation of temperature *per se* increases the ability to utilize sugar.

(*i*) *Infections.*

The ease with which alimentary glycosuria occurs in certain febrile diseases was observed as long ago as 1896 by Poll. The spontaneous and alimentary hyperglycemia present in certain infections, especially pneumonia, was investigated by Liefmann and Stern, Hollinger, and Tachau (1). Hypoglycemia may be found in certain infections, or when the patient's strength fails. Glycosuria has been reported in connection with the following infectious diseases.

Anthrax.
Boils and carbuncles.
Cholera.
Diphtheria.
Dysentery.
Erysipelas.
Erythema nodosum.
Gonorrhea.
Influenza.
Malaria.
Measles.
Mumps.
Pertussis.
Pneumonia.
Rabies.
Scarlatina.
Sepsis.
Syphilis.
Tetanus.
Typhoid.
Typhus.
Vaccinia.
Variola.

All forms of infection by pus-organisms have been known to dispose to glycosuria and to lower the sugar tolerance. Lepine [(3). See also (1), p. 195] reports hyperglycemia produced in a series of dogs by intravenous injections of staphylococcus cultures. The rôle of boils and carbuncles in this connection has been doubted, because of their frequent appearance in early diabetes, so that the lowered tolerance is supposed to be due to the diabetes and not to the infection. But Becker has recently stated that in cases of phlegmons, boils, and carbuncles, having nothing to do with diabetes, spontaneous glycosuria sometimes occurs, and lowered dextrose tolerance is rather frequent. The point is obviously of some diagnostic importance in certain patients who may be suspected of diabetes.

Regarding diphtheria, Hibbard and Morrissey came to the following conclusions. (1) There is often transitory glycosuria in diphtheria; it is found frequently in severe cases and usually in fatal cases. (2) It is often associated with albuminuria. (3) Antitoxin injections are occasionally followed by slight glycosuria for a few days. The authors take asphyxia into consideration as a cause, but consider the diphtheria toxin more important.

Garrod (2) describes a series of cases of mumps with pancreatitis. In one of these, polyuria and glycosuria occurred, but disappeared completely within two weeks. In some cases the condition is evidently a transient diabetes.

Details concerning the other members of the list may be found in the texts of Kleen, Lepine, and Rosenberger. In most of the series, glycosuria is rare. The excreted sugar is not always dextrose. Aside from diphtheria, the highest prevalence is claimed in malaria. Lepine [(1), p. 325] quotes figures of Calmette, showing 5 cases of glycosuria among 41 soldiers with malaria; and of other writers, showing 17 instances of glycosuria among 100 malaria patients without cachexia, and 76 instances among 100 malaria cases with cachexia. There is great discrepancy between different reports and opinions concerning malarial glycosuria.

Parry (ref. by Rosenberger) reported glycosuria in a child with Oxyuris vermicularis, ceasing with the expulsion of the worms. See also D I (d).

Several writers are quoted by Naunyn (p. 148) claiming relatively frequent transient glycosuria in early secondary syphilis, but their complete accuracy is doubted. Syphilis as a cause of diabetes is discussed at considerable length by Naunyn.

(j) Fatigue.

Glycosuria in normal persons from over-exertion is mentioned by Kleen (p. 68). Lepine [(1), p. 318] refers to a report of albuminuria and glycosuria in Marathon runners, but doubts the correctness. He makes the objection that the most extreme fatigue in experimental animals has never been known to cause glycosuria.

2 D II. Peripheral.

Glycosuria from stimulation of peripheral nerves is generally reflex, through afferent stimuli, and therefore central in origin. There are, however, a few forms of glycosuria which depend upon direct stimulation of a peripheral nervous mechanism.

(a) Stimulation of Splanchnic Nerves.

Since the splanchnic nerves are known to carry the impulse which causes glycosuria after puncture of the medulla, it is easy to imagine that stimulation of these nerves will produce a like result. But the failures of early workers, especially Eckhard, are recorded in texts, and are used by Pflüger [(13), also (1), p. 387] as

an illustration of the difficulty and deceptiveness of research in neurology. There must be just the right sort of stimulus, and it must affect the glycogenolytic fibres in preference to their antagonists, etc., in order to obtain positive results. Cavazzani found that stimulation of the cœliac plexus gives rise to hyperglycemia and loss of liver-glycogen. Kahn (2) found that piqûre produces glycosuria, and also a characteristic picture of exhaustion in the adrenals, the result of a central stimulus transmitted through the splanchnic nerves; artificial rhythmic stimulation of a splanchnic nerve causes intense glycosuria, but does not change the adrenal medulla in this manner. Macleod (1) had previously obtained results summarized as follows. Stimulation of the spinal cord at any level fails to cause hyperglycemia when asphyxia is prevented. When both great splanchnic nerves are cut, stimulation of the peripheral ends does not produce hyperglycemia. Stimulation of the left splanchnic nerve, when no nerves are cut, usually produces marked hyperglycemia and glycosuria. In many experiments, the urine acquires distinct reducing properties without there being any hyperglycemia.

As with central, so with peripheral stimulation, the most probable view is that both humoral and direct nervous influences are concerned, and that the stimulation affects not only the adrenals but all viscera within the distribution of the nerve. It is seen, for example, that the permeability of the kidney for sugar is increased, probably by direct nervous influence, for intravenously injected adrenalin has the opposite effect (Pollak).

Clinically, glycosuria and even diabetes are occasionally seen in association with trauma, tumor, or other morbid process somewhere in the splanchnic path. It is possible that direct stimulation of the peripheral mechanism is etiologic in these cases.

(*b*) *Adrenalin.*

Adrenalin is the most important agent which produces glycosuria by direct stimulation of a peripheral mechanism. It will be considered in Chapter XVI.

(*c*) *Drugs and Poisons.*

The possibility exists that other drugs or poisons may cause hyperglycemia through peripheral stimulation. No such substances are demonstrated as yet. But the list of those whose action is still not definitely explained is sufficiently long to justify

leaving a place here open. Adrenalin is merely an alkaloid. According to Starkenstein (3), anæsthetics act upon the same peripheral mechanism as adrenalin, but in the opposite direction. It is hardly probable that adrenalin is the only substance in the world which acts upon this mechanism in the direction of glycosuria.

Since the above was written, Mayer (4) has described a form of glycosuria produced by subcutaneous injection of pyro-racemic acid. After injection of 7–8 g. of the acid in the form of its sodium salt, in rabbits weighing 2–2½ kilos, hyperglycemia and glycosuria regularly begin within 2 hours, and continue for some 24 hours. A small portion of the acid is excreted as such, with lactic acid. The acid produces some glycogen-formation, and is evidently in relation with carbohydrate metabolism. The glycosuria occurs in glycogen-free animals. It is possible that this form of glycosuria discovered by Mayer belongs in the present category. It bears a resemblance to adrenalin in its latent period, and in its occurrence in relatively glycogen-free animals after long fasting; possibly also in stimulating glycogen-formation. Further study will be necessary for decision.

2 D III. Undetermined.

Thyroid.

The relation to glycosuria will be treated in Chapter XIX. The glycosuria is to be regarded as of simple toxic nature; the poison apparently acts through the nervous system, but there is no evidence whether the mechanism is central or peripheral. The action is non-specific. The thyroid is not known to have any share in carbohydrate metabolism. It is not an "antagonist" of the pancreas, and no diabetogenic influence is demonstrable [Chapter XIX]. The present confusing views regarding the thyroid are simplified by understanding that its effects upon the carbohydrate metabolism are not direct; that its internal secretion does not, like that of the pancreas, take part in this metabolism; and that the influence of the thyroid in this respect is only the result of its action upon the nervous system.

Parathyroids.

Thyroid glycosuria is positive, the nervous intoxication being the result of glandular excess. Parathyroid glycosuria is negative,

the nervous intoxication being the result of glandular deficiency. The subject will be treated especially in Chapter XIX. The removal of the parathyroids somehow, perhaps through lack of necessary substances or through accumulation of harmful substances, gives rise to a condition of great nervous over-excitability, called tetany. The slight glycosuria which in a minority of cases accompanies this condition is fully explainable by the nervous excitement. Parathyroidectomy increases adrenalin glycosuria, just as does anything else that favors the nervous stimulation produced by adrenalin. It increases sugar-excretion after pancreatectomy, just as do other forms of nervous stimulation. Parathyroidectomized animals have a very low dextrose tolerance; apparently absorption is also greatly impaired, as evidenced by the prolonged excretion of dextrose observed by Underhill and Saiki; but the whole is part of a severe and fatal cachexia. There is no evidence that the parathyroids "assist" the pancreas. The parathyroids have been assigned a high and mysterious rôle in carbohydrate metabolism. There is no evidence that they take any part whatever in this metabolism, and the understanding of their real functions will be assisted by the dropping of these unfounded notions. This subject is clarified somewhat by the recognition of the fact that the disturbance of the sugar-economy after parathyroidectomy is the result of the cachexia and especially of the nervous excitation. It cannot yet be said positively whether the glycosuria results from central or peripheral stimulation, or both.

Hypophysis.

It was only in 1886 that Marie defined acromegaly, and related it with the hypophysis; yet the immense literature that promptly sprang up is shown in the Sammelreferat by Münzer in 1910, and the activity of the investigation has progressively increased since then. A few of the elementary facts and the relations to glycosuria are all that can be given here. The latest extensive experimental work is by Aschner. The monograph by Cushing gives the best and most recent general review, and is the acme of clinical research on the subject to date. Biedl's standard work is well known, and the subject is also included in Swale Vincent's review of internal secretion in 1911.

The hypophysis consists of two lobes; an anterior, called the epithelial, glandular or pituitary lobe, which is kidney-shaped with the concavity backward; and a smaller, rounded, posterior lobe

of softer tissue, the nervous or infundibular lobe, which lies in the concavity of the anterior lobe. The two lobes are connected, and are inclosed in a common fibrous capsule. The anterior lobe, as its name *epithelial* indicates, consists largely of cells comparable in a broad sense with those of other glands of internal secretion. The posterior lobe is composed of a histologically rather indefinite material, supposedly related to neuroglia. Whether it contains nerve-cells is disputed. The main mass of the posterior lobe comprises the *pars nervosa*, in a strict sense, and this is surrounded by a narrow investment of epithelial cells, generally called the *pars intermedia*. Through the pars intermedia at one point there is a partial fusion of the two lobes.

Paulesco [ref. by Biedl (3)] proved that the hypophysis is an organ necessary to life. Cushing confirmed the fact, and further showed that only the anterior lobe is thus necessary. The removal of this lobe leads to death within a few days or weeks, with a symptom-complex called *cachexia hypophyseopriva*. Puppies survive the operation longer than adult dogs. Injury or partial removal of the anterior lobe permits life, but is followed by symptoms of obesity, loss of hair, failure of sexual function with atrophy of testes or of uterus and ovaries, and sometimes acute hypertrophy of the thyroid. In the posterior lobe can be seen microscopically masses of hyalin or colloid substance described by Herring, and supposed by him to represent secretion destined to be poured into the cavity of the third ventricle. Cushing has supported this view, and experiments and beautiful plates are presented in the paper of Cushing and Goetsch. The posterior lobe is not essential to life, and has been supposed to be removable without symptoms. Part of the symptoms mentioned as following partial removal of the anterior lobe are however now attributed by Cushing to the deficit of posterior lobe secretion. The subject is still doubtful. The metabolism after hypophysectomy has been studied by Benedict and Homans and other authors; the processes are slowed, somewhat as after thyroidectomy. Aschner (2) has found that adrenalin produces very little effect in such animals; not only is glycosuria very slight, but, what may be considered more remarkable, the local necrosis ordinarily resulting from the subcutaneous injection is said not to occur.

With regard to hypophyseal extracts, somewhat of a paradox appears, for the anterior lobe, the one essential to life, furnishes

an extract which is relatively inert. Cushing credits it with the power of temporarily warding off cachexia hypophyseopriva. The effects upon growth, stated by some authors to be produced by feeding this lobe to young animals, were not supported by the recent work of Aldrich. The posterior lobe yields an extract broadly resembling adrenalin in properties, but less powerful and differing in several particulars. It not only increases blood-pressure but also causes polyuria, when given either intravenously or subcutaneously. It has a certain influence in accelerating metabolism in normal or acromegalic persons, and long-continued administration leads to emaciation in experimental animals. Borchardt (2) found that protein-free extracts of horse or human hypophyses (both lobes) caused slight, transient glycosuria in 23 out of 30 experiments on 5 rabbits. His experiments with dogs were a failure, except in one partially depancreatized animal soon after the operation. Rossi [ref. by Franchini] confirmed Borchardt. Franchini on the contrary obtained entirely negative results. Falta, Newburgh and Nobel found that though this extract produces increased blood-pressure and diuresis, it does not cause glycosuria in either dogs or rabbits, nor increase the sugar-excretion of depancreatized dogs. Goetsch, Cushing and Jacobson have regularly obtained glycosuria from injections of the extract in normal rabbits. In dogs they have claimed that the extract lowers sugar-tolerance. They explain discrepant results on the basis of different modes of preparing the extract. Von Noorden [(1), p. 52] thinks anterior-lobe products in Borchardt's extract explain his findings. But another source of difference may be more important, viz., the rabbits. Full-fed, glycogen-rich rabbits are known to be frequently very susceptible to glycosuria from almost any cause, and there are differences between different strains. Glycosuria obtainable only in rabbits and absent in other species may safely be considered to be without special significance. The negative findings of Franchini and Falta in rabbits, and of other investigators in dogs, exclude the possibility of looking upon hypophyseal extract as a true glycosuric agent like adrenalin. Falta has found that hypophyseal extract increases adrenalin glycosuria; and Kepinow has reported that it augments the vasomotor and mydriatic effects of adrenalin, by sensitizing the point of attack. Others have considered that the point of attack is different, and that hypophyseal extract has a direct action, like barium chloride [cf. E. Frank].

The principal clinical expressions of hypophyseal disorder are acromegaly, gigantism, and conditions of infantilism (with asexual and contra-sexual characteristics), obesity (dystrophia adiposo-genitalis, adiposis dolorosa), etc. Hewlett has a recent paper on certain types of the infantilism. E. Frank has brought the hypophysis strongly into prominence for the etiology of diabetes insipidus. The eosinophilic hypophyseal adenoma is considered typical of acromegaly, but Erdheim reported a case of basophilic adenoma without signs or symptoms of acromegaly. The symptoms of over-function and under-function of the gland and its different parts are still under study. An extract of the posterior lobe is on the market, under the name of pituitrin or hypophysin,* and is used in the therapy of hypophyseal disorders. The benefit from its proper use is well established; the success is not, however, comparable to that of thyroid extract in myxœdema. A more brilliant success has been claimed for it within recent months as an aid in childbirth, for stimulating contractions. Its experimental vascular and respiratory effects have been investigated by a series of authors, the most recent Paukow.

Von Noorden [(1), p. 52] refers to the extraordinary frequency of glycosuria in acromegaly. The early figures placed it at 10–12 per cent of all acromegaly cases, but it is much more common than that. Borchardt (3) reckons it at nearly 40 per cent of all cases. The glycosuria in acromegaly is subject to great variations, and is not governed by the diet as regularly as the glycosuria in diabetes. On the other hand, the slight effects of adrenalin in hypophysectomized dogs are supposed to furnish an analogy for the high carbohydrate tolerance of patients with hypopituitary obesity.

Lepine [(1), p. 439] agrees as to the frequency of diabetes in acromegalics, and states that there is generally no doubt as to the order of precedence; the acromegaly has often been present for some time, while the diabetes comes on considerably later. The glycosuria may be intermittent. The acromegalic diabetes is relatively benign in course. Acetonuria is recorded in a few instances, but it is rare. Lepine has learned of only one patient with acromegaly who died in coma. There can be no question that it is true diabetes, for the sugar-excretion is high. Reference is made to reports concerning diabetic patients with acromegaly, who excreted 200 to 1200 grams of sugar per day, with a polyuria

* Cushing suggests that the extract of the anterior lobe should be called pituitin, of the posterior lobe infundibulin, and of the entire gland hypophysin.

of 3, 6, 8, and in one case 20 litres per day. Lipemia was reported in one acromegalic. Opinions are divided concerning the cause of acromegalic diabetes. Some consider it due to tumor or other abnormal process about the hypophysis, disturbing the centres which govern the pancreas. Lepine is more disposed to believe that it is due to a perversion of internal secretion of the hypophysis.

Goetsch, Cushing and Jacobson, continuing the earlier studies from Cushing's laboratory [see Crowe, Cushing and Homans, and Cushing and Goetsch] have supported Herring's view that the posterior lobe of the hypophysis elaborates a colloid secretion, which is stored in the infundibulum and hypophyseal stalk, and gradually excreted into the third ventricle, with the result that it can be demonstrated by suitable tests in the cerebro-spinal fluid. It is possible to perform operations upon the hypophysis — for example a clean-cut removal of the posterior lobe — without resulting glycosuria. But any form of operation which involves injury or extensive manipulation of the infundibulum and hypophyseal stalk results in setting free an excess of the secretion, and is accordingly followed by slight glycosuria for a day or two, and a lowered carbohydrate tolerance for several days thereafter. If the posterior lobe is removed or the discharge of its secretion blocked, the above temporary effect is followed by an increase of sugar-tolerance, even to twice the normal. The sugar-tolerance of these animals, or of normal dogs, is easily lowered by subcutaneous or intravenous injection of posterior lobe extract. Along with the increased sugar-tolerance, there is a tendency to general obesity. This, and the emaciation following repeated injections of the extract, caused Cushing to change his former view, and to believe that part of the symptoms formerly credited to the anterior lobe are due to lack of the secretion of the posterior lobe. The early active stages of clinical acromegaly or gigantism are found to be commonly associated with glycosuria or lowered carbohydrate tolerance. Since the clinical just as the experimental lesion often produces polyuria, the condition may be readily mistaken for diabetes mellitus or insipidus. But in later stages the patient has passed from hyper- to hypo-pituitarism, therefore the deficiency of posterior lobe secretion should result in an elevated assimilation limit for sugar; and a series of clinical case-records are presented to show that this expectation is fulfilled. Patients with dyspituitarism show an abnormally high tolerance for dextrose, and a somewhat less marked increase for levulose.

Treatment with glandular extract is indicated at this stage, and the dosage may perhaps be determined by the amount necessary to reduce the sugar-tolerance to normal.

Carlson and Martin disproved the claim that the normal cerebro-spinal fluid of dogs shows any pressor effects or lowers the sugar tolerance when injected intravenously into other dogs. The positive findings of Cushing and Goetsch are explained as due to the injection of large quantities of concentrated human cerebro-spinal fluid into rabbits; the pathological nature and especially the foreign origin of the fluid are important. Also, as against the claim that simple handling or injury of the hypophysis in operations may press out enough secretion to give rise to glycosuria, they showed that injections or implantations of two to ten entire glands or the separate lobes fail to cause glycosuria; the post-operative glycosuria mentioned is therefore due to nervous injury.

In unpublished experiments by Pratt, the statement that removal of the posterior lobe of the hypophysis, after an initial lowering, gives rise to an increase of sugar-tolerance, was not confirmed. In one dog (operation by Homans), the observation was extended to a year after the operation; at the end of this period the subcutaneous tolerance was only 2 g. dextrose per kilo, *i.e.*, about one-fourth the normal. Positive judgment is deferred, since the question whether the operation was a simple posterior-lobe removal, and other questions concerning this single animal, require further investigation.

The subject is obviously confused. Points to be considered are the effects of extracts, the effects of removal of the posterior lobe, and the relation of the hypophysis to diabetes. Concerning the first, there is sufficient evidence that the extract or implantation of the posterior lobe or of the entire gland fails to give rise to any specific glycosuria. The glycosuria observed after certain hypophyseal operations cannot be attributed to the setting free of substances contained in the gland, for it is agreed by all that the introduction of the fresh gland-substance or extract fails to cause glycosuria in dogs, which are the animals in question. A lowering of the carbohydrate tolerance and an increased tendency to glycosuria would not be surprising, since the extract has been found to augment the effects of adrenalin. There is as yet none but the anatomical evidence in favor of the view that the hypophysis discharges a secretion into the cerebrospinal fluid. The reason may be that no reliable tests for the presence of such a

secretion are yet known. With regard to the effects of both the gland-extract and the cerebrospinal fluid upon the sugar-tolerance, there may still be a profitable field open. It is unfortunate that so much of this investigation has been conducted on the basis of untrustworthy tests of the tolerance. Finally, it may be suggested that if the hypophyseal secretion is normally discharged into the cerebrospinal fluid, the imitation of this natural process is obtained not by injecting the extract intravenously or elsewhere, but by injecting it into the cerebrospinal fluid. It is conceivable that the action may be directly upon the nervous structures.

With regard to the effect of posterior-lobe extirpation upon the sugar-tolerance, it is conceivable that slight differences in operative methods might give diverse results; but one source of discrepancy probably lies in the methods of testing the tolerance. The diminished tolerance reported by Pratt was demonstrated by the feeding and subcutaneous injection of dextrose, and further experiments of this nature are desirable. The Blumenthal test, which places a premium upon the permeability of the kidney, is probably not reliable for use in a condition where the renal function may be altered. The return toward normal tolerance, observed by this method after injections of hypophyseal extract, may be interpreted simply as part of the diuretic effect, an increase of permeability. The test by cane-sugar feeding is not dependable, and is especially unsuitable under these conditions. Even normal dogs may vary widely in the proportions of reducing sugar and saccharose excreted. What the possibilities are when internal secretory organs are disturbed is indicated by the remarkable observation of Hirsch mentioned in Chapter II, viz., after feeding of amylodextrin, the excretion of the unchanged dextrin in the urine by thyroidectomized dogs. An abnormal behavior toward cane-sugar is much easier to suppose. Goetsch, Cushing and Jacobson mention no tests for saccharose in the urine. In the case of their Dog 35, most of the pancreas was removed; the autopsy showed "the only remaining pancreatic tissue to be a small piece attached to the duodenum." The cane-sugar tolerance soon rose to normal, and after partial hypophysectomy increased to twice normal. Inasmuch as accurate tests prove that a dog with only a small fraction of pancreas remaining has invariably a lowered sugar-tolerance, it is evident that the test in this instance was faulty; and since it was so in one case, there is the possibility

that it was so in all. Saccharose may have been excreted in the feces or urine, without the presence of reducing sugar in the urine. Incidentally, it would be of interest to know whether the kidney of the dog with partial hypophysectomy inverts parenterally injected saccharose as does the kidney of the normal dog. As for increase of tolerance above the normal in a dog with only a small pancreatic remnant, it may be predicted that such a result will be found impossible by any sort of procedure with any or all of the organs of the body; such procedures may impair the absorption or excretion of sugar, but it is doubtful if the actual utilization in such a partially depancreatized animal can be raised even to normal. In patients with certain hypophyseal disorders, it would not be surprising if there were an actual increase of assimilation, but it is not yet demonstrated that the supposed increase represents anything but delayed absorption and impaired excretion. Accurate information concerning the rate of utilization of sugar by the tissues might be obtained by injection subcutaneously, where the absorption is perhaps less altered than in the intestine; as a control, prolonged intravenous injections at a definite rate might be of service; and controls of the renal function by blood-sugar tests would in all cases be indicated. Similar methods might be of interest to test the supposed increase of assimilation in hypothyroidism or Addison's disease.

The relation of the hypophysis to diabetes will be considered in Chapter XIX. Existing views regarding a specific relation are not plausible, since they place the hypophysis with the thyroid and adrenals as imaginary "antagonists" of the pancreas. A very important field of research is here open. Later chapters will illustrate the value of partially depancreatized dogs as test-objects for influences in relation with diabetes. If a given influence tends to produce diabetes, then it should actually produce it in an animal brought sufficiently close to the verge of diabetes by removal of a suitable portion of pancreatic tissue. If a given influence tends to prevent diabetes, it should prevent it in an animal depancreatized to such a degree as barely produces diabetes under normal conditions. There is hope that the relation of the hypophysis to diabetes may be cleared up by investigation along these lines. In particular, since the carbohydrate tolerance is lowered by partial hypophysectomy, even to the point of spontaneous glycosuria following the operation, there is the possibility that diabetes might result in an animal suitably predisposed by partial

pancreatectomy. The single experiment in Cushing's laboratory tends to make it doubtful whether the hypophysis has even this slight influence with respect to diabetes, but the point is not settled decisively. In general, it is probable that the nervous outweigh the humoral influences of the hypophysis as respects glycosuria. It is not yet demonstrated that the hypophysis supplies any internal secretion of specific importance in carbohydrate metabolism. Clinically, diabetes with hypophyseal troubles is best explained as due to associated functional or organic disorder of the pancreas. Experimentally, it is possible that functional changes in an organically weakened pancreas may be demonstrable as a result of operations upon or about the hypophysis. The best evidence at present serves to classify the hypophysis among the central nervous causes of glycosuria.

Ligature of Thoracic Duct.

Gaglio [ref. by Naunyn, p. 116] claimed that ligature of the thoracic duct prevents glycosuria after total pancreatectomy in dogs. He drew incorrect conclusions regarding the nature of diabetes. Lepine [ref. by Naunyn, p. 116] on the contrary witnessed glycosuria after ligating the thoracic duct in normal animals, and an increase of the sugar excretion in depancreatized dogs. Gerhardt (quoted by Naunyn) obtained no glycosuria by ligating the duct in normal animals. Tuckett (1) claimed that injection of lymph of fasting animals into the portal circulation is without effect, but lymph of digesting animals causes hyperglycemia of 0.3 to 0.9 per cent, and glycosuria of 1 to 9 per cent. Kleen (p. 193) mentions experiments of Lepine, in which injection of duct-lymph diminished glycosuria in depancreatized dogs. The experiments of Biedl require more detailed mention.

Biedl (1) reported that of 62 dogs with ligation of the thoracic duct, 42 (66.6 per cent) developed glycosuria. Of 90 dogs with fistula of the duct, 78 (86.6 per cent) showed glycosuria. The glycosuria was independent of food, and fairly lasting, with a slow diminution. The longest duration was 3 months. Sugar excretion began $\frac{1}{2}$ hour, at latest $1\frac{1}{2}$ hours after operation, and continued even while fasting. It was generally between 1 and 2 per cent, but in one case was as high as 5.8 per cent. More or less polyuria accompanied the glycosuria. Hunger, thirst, and other diabetic symptoms were not present. In a few cases, ligation of the right lymphatic duct was done at a later operation,

and this duct was found markedly dilated. Biedl thinks the enlargement means compensation for the thoracic duct through side-branches; and to this collateral circulation he attributes the negative cases, and the slow decline of the glycosuria in positive cases. Only 5 of his series showed chylous ascites, hence he concludes that collateral lymph-channels were present in all the other cases. Ligation of the right thoracic duct caused renewed glycosuria. With very few exceptions, the pancreas was found normal at autopsy. Contrary to Gaglio, ligation of the thoracic duct failed to prevent glycosuria after pancreatectomy. The author concludes that glycosuria following ligation of the thoracic duct has no connection with the pancreas, but that the duct-lymph seems to contain a substance which directly or indirectly influences the utilization of sugar in the body. Yet intravenous injection of lymph in a dog with thoracic-duct glycosuria did not stop the glycosuria.

Schlesinger (1) found in dogs a marked lowering of sugar-tolerance after tying the thoracic duct. There was a similar reduction after tying the bile-duct, and a still greater reduction after tying both ducts. The behavior to levulose was as in diabetes, first excretion of pure levulose, later excretion of only dextrose, or a mixture. But in later stages in these animals, a greatly increased tolerance for dextrose developed; Schlesinger explained this erroneously on the basis of the supposed lymphatic absorption of sugar.

Biedl (2) was leader of the discussion on Schlesinger's paper, and offered numerous criticisms. Absence of spontaneous glycosuria after ligation of the thoracic duct was explained by the assumption of collateral lymph-trunks. Others present cited clinical cases in which obstruction of the thoracic duct was associated with glycosuria.

Tuckett (2) modifies his previous attitude, in that he now concludes that there is no evidence that lack of the internal secretion of the pancreas is a factor in certain forms of experimental glycosuria, nor that carbohydrate diet increases the internal secretion of the pancreas. He attributes thoracic duct glycosuria to the anæsthetic or to nerve-stimulation.

Wilms has reported cases of human fat-embolism, in which life is claimed to have been saved by drainage of the thoracic duct. The lymph of these fasting patients is stated to have contained large drops of fat. No mention is made of glycosuria, and as the

patients were in hospital, we may perhaps infer that it would have been noted if present.

Biedl's investigation was continued by Biedl and Offer. The lymph was found to possess diastatic and glycolytic activity. Dogs with thoracic-duct glycosuria show the Loewi adrenalin-mydriasis. Lymph inhibits the Meltzer-Ehrmann adrenalin reaction of the frog's eye. Dogs with duct-fistula were injected with hirudin intravenously, and thus large quantities of incoagulable lymph were obtained. This lymph failed to neutralize the pressor effects of adrenalin, but adrenalin glycosuria was prevented or diminished by injection of lymph. The dose of lymph necessary for this inhibition was generally 80–120 cc., but one very active lymph showed perceptible effects in doses of 15 cc. Lymph freed from albumin by alcohol showed similar properties. The experiments and conclusions are directed in favor of a relation between thoracic-duct glycosuria and diabetes.

The departure from Biedl's previous sound conclusions is one of the numerous unfortunate results of the polyglandular doctrine. There is sufficient evidence to prove that the internal secretion of the pancreas does not enter the circulation through the lymph; incidentally, the injection of lymph has failed to modify either the thoracic-duct glycosuria or diabetes. The notion of "antagonisms" has since fallen. That the above glycosuria is not diabetic is demonstrated by two facts: (1) The time of onset. This slight glycosuria sometimes begins ½ hour after operation, *i.e.*, sooner than after total pancreatectomy. (2) The character of the glycosuria. If this is diabetes at all, it is diabetes gravis, for the dogs excrete sugar even when fasting. But any diabetic dog that excretes sugar when fasting has a very heavy glycosuria on meat diet and an enormous glycosuria on carbohydrate diet. There are no exceptions; hence Biedl's dogs were not diabetic. The facts may be more conclusively established by tests of the paradoxical law and diuretic properties of dextrose during the glycosuria. In particular, nervous or other polyuria is distinguished from diabetic polyuria by the failure of dextrose to increase it.

The condition cannot be due to intoxication by lymph-stasis, since it occurs when the duct is drained. It cannot be due to lack of lymph, for injection of lymph does not stop it. Two facts tend to classify it as nervous: (1) The adrenalin-mydriasis phenomenon, which is a sign of sympathetic excitement. (2) The different results of different workers, indicating that the different

operative methods may be of influence. The important nerves not far from the thoracic duct may perhaps furnish the explanation. It is desirable that this interesting form of glycosuria should be tried in partially depancreatized dogs, which have a greater tendency to most forms of glycosuria than normal dogs. It is conceivable that the sympathetic irritation here present might produce diabetes in animals sufficiently close to the verge.

Clinically, thoracic duct glycosuria comes into importance in analogy with the glycosuria which is frequent in both European and tropical chyluria. Magnus-Levy (3) calls attention to the frequency, and draws the comparison. Naunyn, on the other hand, has classified this type as a renal glycosuria. Analyses of the blood-sugar will decide this point, and apparently such have not been made.

Pregnancy.

It is possible that the glycosuria and lowered sugar-tolerance of pregnancy are to be classified among the nervous glycosurias. The slight intoxication is one possible cause. There is no evidence whether the mechanism is central or peripheral.

Tumors.

Neoplasmic formations in various nerve-paths are known occasionally to cause more or less glycosuria. Presumably the mechanism may be peripheral or central, according to location. Tumors of the female sexual organs are said to be sometimes associated with a slight glycosuria.

Adolescence.

Glycosuria as a rare phenomenon of adolescence is mentioned by occasional authors. Practically nothing is known concerning it, but it may be classified with probability among the nervous disturbances of that period.

Gout.

The connection between gout and diabetes, in the same family or the same individual, is mentioned in all texts; but the present paragraph refers not so much to this connection as to the occasional transient glycosuria accompanying gouty attacks in non-diabetic patients. Nothing can be said concerning the cause except that it is unknown.

The chapters immediately following will take up, in order, successive representative types of glycosuria in this classification, in connection with which experiments are to be presented.

CHAPTER XIII.

ALIMENTARY GLYCOSURIA AND DIABETES.

THE problem begun in Chapter III, concerning the influence of long-continued excess of sugar in producing diabetes, is best studied in animals with lowered tolerance. Easy alimentary glycosuria is obtainable in dogs by starvation, and especially by partial pancreatectomy; furthermore, the two influences can be combined. By suitable tests, it is possible to determine the relations of alimentary glycosuria and also of "hunger glycosuria" to diabetes.

The material may be presented in three divisions:

1. Hunger glycosuria.
2. Acquired tolerance.
3. Prolonged excess of sugar.

1. Hunger Glycosuria.

The discovery of this condition by Hofmeister has been mentioned in Chapter I. It seems to be limited to dogs and to man. In fasting cats, guinea-pigs and rats I have found no marked tendency to glycosuria even in most advanced weakness; in particular, the subcutaneous tolerance of cats as reckoned on the body-weight seems to be little changed till the animal is at the verge of death. Fichtenmayer's rabbits assimilated enormous doses of dextrose without glycosuria, even up to death. One experience indicates that chronic malnutrition may be more effective than acute starvation; for in one cat brought to the laboratory nearly dead from prolonged under-nourishment, glycosuria could be produced by the subcutaneous injection of 3 or 4 g. dextrose, and this low tolerance persisted for some two weeks while the animal was still feeble. After another month of good care, the tolerance had risen to about 10 g., which was the normal. In man, this form of glycosuria was first described by Hoppe-Seyler; tramps, entering the hospital after long insufficient diet, sometimes show glycosuria for the first day or two on mixed diet.

but it promptly disappears. De Dominicis explained diabetes as the result of impaired nutrition, due to absence of pancreatic juice from the bowel. Hinselmann (2), though acknowledging the insuperable obstacles presented by the pancreas-graft experiments of Minkowski and Hedon, still suggests the possible validity of the De Dominicis hypothesis, and attempts to support it by analogy with the "hunger," "vagabond," and "duodenal" forms of glycosuria. An appearance of support for some of the hypotheses may be found in the work of Statkewitsch, who reported that glandular tissues suffer earlier and greater changes in starvation than muscular tissue; among glands, a descending order of changes are shown by the liver, kidneys, parotid, submaxillary, and last the pancreas; the cells of the acini shrink, and become little "heaps," resembling islands of Langerhans.

It has been necessary to omit the protocols of the following experiments, which therefore are presented in summarized form. A few experiments dealing with the effects of water are omitted. Some have supposed that a large quantity of water given with the sugar may conduce to glycosuria; but in these few experiments, no influence of the water was perceptible. The greatest variation is in the dogs; some show the lowering of tolerance earlier than others. All the following animals were catheterized at fixed hours twice daily.

Dog 18; white bull terrier; female; age 2 years; weight 8 kilos; good nutrition.

November 25, starvation begun.

December 19, weight 5380. Temperature 97°. Dextrose 1 g. per kilo by mouth. Glycosuria faint.

December 20, weight 5240. Temperature 97°. Dextrose 2 g. per kilo by mouth. Glycosuria slight.

December 22, weight 5090. Temperature 97. Subcutaneous injection of dextrose equal to the dose fed on December 19. No glycosuria.

December 23, weight 5020. Temperature 96°. Subcutaneous injection of dextrose equal to the dose fed on December 20. Glycosuria very faint.

Wherever any effect of the small doses of dextrose upon the urine was perceptible, it was in the direction of diminution.

Dog 22; white fox terrier; female; age 3 years; weight 6300 g., medium flesh.

December 18, starvation begun. Dog receives water entirely by tube, 100 cc. at 9:30 a.m. and the same at 4:30 p.m.

January 2, weight 4720. Temperature 100. Dextrose 1 g. per kilo given with morning water. No glycosuria.

January 3, weight 4705. Temperature 99^6. Dextrose 2 g. per kilo given with morning water. Glycosuria 0.7 per cent = 0.53 g.

January 4, weight 4750. Temperature 98^6. Subcutaneous injection of dextrose equal to the dose fed on January 2. No glycosuria.

January 5, weight 4600. Temperature 98^8. Subcutaneous injection of dextrose equal to the dose fed on January 3. Glycosuria 0.48 per cent = 0.336 g.

January 7, weight 4450. Temperature 98^2. Subcutaneous injection of 10 g. dextrose per kilo. Glycosuria that evening 5.6 per cent; the next morning 0.6 per cent. Total excretion = 4.55 g. Anti-diuretic effects as usual.

In normal dogs, the oral dextrose tolerance on an empty stomach is somewhat greater than the subcutaneous tolerance. The experiments with Dogs 18 and 22 show how this relation is reversed in starvation, and for some reason the subcutaneous is slightly higher than the oral tolerance. The great reduction of tolerance by both tests is evident, down as low as 1–2 g. per kilo, *i.e.*, $\frac{1}{8}$–$\frac{1}{4}$ the normal. I regret that comparative experiments with the Blumenthal intravenous test were not possible. It will probably be found that this test as usual fails to show the true state of the assimilative power.

Dog 17; mongrel, brindle and white; female; age 2 years; weight $8\frac{1}{2}$ kilos, medium flesh.

November 27, starvation begun.

December 14, weight 6150. Temperature 100^2. Subcutaneous injection of 10 g. dextrose per kilo at 1 p.m. Dextrose excretion, evening urine 0.85 per cent = 0.765 g.; next morning 1.2 per cent = 1.85 g.; total = 2.615 g. Anti-diuretic effect as usual.

The experiments with all these dogs show that the paradoxical law and anti-diuretic properties of dextrose are fully retained

during hunger glycosuria. The apparent tolerance is very low; the real tolerance, as in all non-diabetic conditions, is infinite. The excretion of dextrose after the large dose of 10 g. per kilo is only a little greater than that of normal dogs. The sugar is firmly bound, as proved by the anti-diuretic action. The ease with which a slight glycosuria is produced is the result not of deficient binding of the sugar, but of a slight slowness of the weakened cells in assimilating sugar.

Dog 17.

March 9, removal of nearly $\frac{5}{6}$ of pancreas.

March 17, weight 9220. Starvation begun.

March 24, weight 7660. Temperature 100^8. Subcutaneous injection 2 g. dextrose per kilo. Glycosuria 1.2 per cent = 0.24 g. Anti-diuretic effect.

March 27, weight 7330. Temperature 100^8. Subcutaneous injection of 6 g. dextrose per kilo. Glycosuria 5.6 per cent = 2.52 g. Anti-diuretic effect.

March 29 to April 3, feeding of nothing but scraps of sweet cake, with the largest possible quantities of glucose and cane sugar. Profuse continual diarrhea; glycosuria slight or heavy according to dosage, ceasing very promptly. The absence of anything like diabetes is shown by the increase of weight, from 7190 g. on March 29 to 8730 g. on April 3 (weighed in morning before feeding).

Therefore, though by fasting, in a partially depancreatized dog, the dextrose tolerance can be brought very low, the condition is not diabetes and shows no diabetic tendency. The sugar is still a colloid, as proved by the anti-diuretic action. The amount excreted is larger than in a normal fasting dog, but the paradoxical law is still fully evident, and the true tolerance is still infinite.

2. Acquired Tolerance.

Dog 32.

Boston terrier mongrel; female; brindle; age 2 years; weight 6400 g., rather fat.

February 14, removal of pancreatic tissue weighing 12.4 g. Remnant about lesser duct estimated at 1.8 g. Duct ligated.

March 6, weight 5830. Diet of sweetened cakes begun. Slight glycosuria. Diet continued till March 31. Glycosuria soon diminished, and after March 12 none was present. Weight April 1, 5890.

April 1–22, diet bread-and-meat mixture. No glycosuria. Weight April 22, 6120.

April 23 to May 2, same diet, and 100 cc. 50 per cent glucose by stomach-tube once daily. At first, glycosuria as high as 2.1 per cent, diminishing to traces. No glycosuria after April 29. Copious diarrhea. On May 1, feces contained abundant dextrose. Weight April 30, 6060; May 1, 6020; May 2, 5850.

The apparent increase of tolerance in this dog was evidently due to diminished absorption. Experience with other dogs of this type has been similar. This condition should be distinguished from the true increase of tolerance which frequently, perhaps regularly, occurs in dogs depancreatized to suitable degree, when the ducts are ligated. Such animals shortly after operation may show spontaneous glycosuria, or glycosuria *ex amylo*. Later they may be able to live on bread without glycosuria, and may show a considerable sugar-tolerance. Finally, if enough pancreatic tissue has been removed, the tolerance sinks, and the end is a fatal Sandmeyer diabetes. The phenomenon of increased tolerance was noted by Minkowski in such animals. The theory is discussed in Chapter XXII. A good example is Dog 173 [see protocol in Appendix], which shortly after removal of most of the pancreas was glycosuric on bread-and-meat diet; later half the existing pancreatic remnant was removed, and yet the dog became able to live on bread-and-meat mixture without glycosuria. This increase of tolerance is not a reaction to sugar treatment, and occurs irrespective of the kind of diet on which the dog is kept.

3. Prolonged Excess of Sugar.

Several authors in the past have tried feeding partially depancreatized dogs with sugar or carbohydrate food for longer or shorter periods, with negative results as concerns the production of diabetes. But in their animals the pancreatic ducts had always been closed. Such animals are prone to disturbances of absorption, so that in forced feeding with sugar, diarrhea predominates over glycosuria, as illustrated by Dog 32. For this reason, and for more important reasons discussed in Chapter XXII, such dogs are unsuitable for this purpose, and the negative results obtained with them possess only negative importance. Even when the pancreatic ducts are left patent, the daily feeding of large quantities of sugar readily gives rise to diarrhea and finally vomiting. Subcutaneous injections avoid these difficulties and are worthy

of a more extended trial than I have given them with partially depancreatized animals. But considerable doses are necessary to produce a continuous and well-marked glycosuria in non-diabetic animals, and the health of dogs may suffer. These difficulties do not exist when the dogs are depancreatized to the point of diabetes levis; *i.e.*, when they show glycosuria *ex amylo*, with the pancreatic duct patent. The starchy diet does not produce diarrhea, and the sugar-excretion may be high, yet ceases promptly on return to meat diet. The condition is the result of a surgical operation; it is not a spontaneous disease like human diabetes. The question then is whether under these circumstances, a continued excess of circulating sugar will break down the tolerance and bring on a condition of severe diabetes, in which sugar is excreted on meat diet.

The pioneers in this highly important field are Thiroloix and Jacob (4). They report positive results. In the milder type of diabetes which they produced, they claim that the animals "during several months (5 to 8) show nothing but a very marked diminution of power of fixing carbohydrate. The ingestion of small doses of carbohydrate gives rise to a sharp increase of glycemia and a heavy excretion of glucose. The glycosuric crises are at first suppressible by meat diet. Later, prolonged carbohydrate feeding leads to insuppressible glycosuria, with emaciation." In other words, Thiroloix and Jacob assert that carbohydrate feeding changes diabetes levis into gravis; that animals which after operation excrete sugar only on carbohydrate diet can by continuance of that diet be brought to excrete sugar on meat feeding. In their brief communication, they do not mention any adequate controls, to prove that similar dogs on meat diet may not have a similar downward tendency, *i.e.*, that glycosuria on meat diet may not supervene after approximately the same length of time, irrespective whether carbohydrate is fed or not. It has not been feasible for me to undertake a definite research covering this point, for a considerable number of animals must be used in order to make the results convincing, on account of the variations among individual dogs after such operations. None of the observations here described are as long or as positive as those mentioned by Thiroloix and Jacob. The impression gained, however, is in favor of the correctness of their position, viz., that the condition in these dogs is aggravated by carbohydrate diet, like human diabetes. The following experiments contribute a few new features not mentioned by Thiroloix and Jacob.

Dog 80; female; age 7 months; weight 4430 g.

September 1, removal of pancreatic tissue weighing 7.9 g. Remnants communicating with both ducts, also one isolated clump; total weight about 1 g.

There was no glycosuria till bread feeding was begun on the tenth day after operation. The sugar excretion was then considerable at first (4.9 per cent), but rapidly diminished, though the gain of weight proved that absorption of food was adequate. Glycosuria ceased on meat diet. On September 23, a return to bread-and-meat mixture produced first a faint glycosuria, then none. In other words, the condition was transient diabetes levis.

On September 25, starvation was begun, in order to bring about hunger-glycosuria. By October 7, the little dog was dangerously weak. Heavy feeding with bread, milk, and sugar caused heavy glycosuria, but by October 10, *i.e.*, as soon as bread-and-meat mixture was fed without sugar, glycosuria ceased, and continued absent thereafter.

Dog 74.

August 19, partial pancreatectomy was performed. The remnant was estimated at exactly one-sixth of the pancreas. There was no glycosuria. On the days following August 23, the dog was able to take moderate quantities of bread and milk without glycosuria.

September 7, diet of bread-and-meat mixture was begun. Huge amounts were eaten, and the dog gained weight very rapidly. Glycosuria also appeared. The manner of its onset is noteworthy, for it is typical under certain conditions. If the pancreas remnant is too large, bread feeding causes no glycosuria; if the remnant is too small, it causes glycosuria promptly; but if the remnant happens to be of just the right intermediate size, the glycosuria is delayed for several days, and then generally comes suddenly and heavily. Thus, here, there was no glycosuria till September 10; then it was 5.2 per cent; on September 11, 4.6 per cent; on September 12, 6 per cent, etc. Deficient absorption is not the reason, as this dog's rapid gain of weight proves. The most reasonable interpretation is that the sugar-free animal, like the sugar-free human diabetic, accumulates a certain store of pancreatic amboceptor. The carbohydrate feeding draws upon this

store, but for a day or two it can stand the drain. After that comes the glycosuria.

September 17–22, still on the same diet and still gaining weight, the dog now showed much less glycosuria. By September 24–25, the same diet had lost its power to produce glycosuria.

On September 25, therefore, starvation was begun, for the sake of hunger-glycosuria. By October 9, the dog was weak and emaciated. [Is starvation more rapidly fatal in partially depancreatized than in normal animals?] Feeding of bread and sugar was therefore begun, and continued till October 19. As soon as the sugar-feeding was stopped on that date, the bread failed to cause glycosuria.

On October 20, an operation was performed to test the effect of simple trauma upon the pancreas. It revealed the reason why the tolerance had risen, so that bread was no longer able to produce glycosuria. The remnant of 2.3 g. which had originally been left, now weighed 4 g. at the lowest estimate. The remnant was dissected free from everything except its duct and vessels. The operation apparently produced a little lowering of tolerance, though it is hard to say, because the glycosuria of the succeeding days was nearly all the result of sugar-feeding, and the glycosuria from plain bread-and-meat fed on October 27 may be explained by the two days of starvation preceding. At any rate, the operation plus the sugar-feeding failed to produce diabetes gravis, for the glycosuria diminished, and as soon as meat-diet was begun on November 7, it disappeared altogether.

The net result is that during a period of three months, with sugar-feeding and other influences to lower tolerance, the dog failed to lapse into diabetes gravis. Diabetes levis existed just after the first operation, then disappeared (September 24–25). Starvation brought it back temporarily, and it again disappeared as soon as weight was regained (October 20). My experience here and in other cases indicates that the gain in tolerance (with patent ducts) is due to actual pancreatic hypertrophy. The tolerance thus gained has never been lost in any animal that I have observed. When a dog has ceased to show glycosuria on bread-feeding, continuance of the bread feeding does not cause him to show glycosuria at some later time. If tolerance is to be broken down at all, it must be in animals which can be induced to maintain a permanent glycosuria. For this purpose, the size of the pancreas-remnant must be smaller.

Dog 86; female; age 1½ years; weight 6890 g.

September 8, removal of pancreatic tissue weighing 13.75 g. Remnant communicating with main duct estimated at 1.6 or 1.7 g. Here the remnant was about one-ninth of the pancreas. Transient diabetes gravis followed the operation. As usual in such cases, heavy glycosuria was produced by bread feeding (September 25). But there was still some tolerance of starch, for on October 5 glycosuria ceased temporarily as a result of diminished appetite. The beginning of meat feeding on October 10 showed that diabetes gravis was not present but perhaps approaching, for glycosuria, though persisting, was rapidly diminishing and would have been gone by October 13, had not bread and meat diet been resumed. The death of the animal from distemper caused failure of an experiment in which a positive outcome was confidently expected.

Dog 20; female; age 11 months; weight 5635 g.

December 7, removal of pancreatic tissue weighing 14.7 g. Remnant about lesser duct guessed at approximately 3 g. (probably too high). On the evening before, the dog had received 100 g. glucose by stomach-tube, and the urine in the cage prior to operation was heavy with sugar. No effect upon the course of events was observed from the sugar. This was an example of slow onset of glycosuria. It was absent from the time of operation till December 10. Then a quart of sour milk was fed, with resulting heavy glycosuria on December 11. After two more days of fasting, a liberal meat diet was begun on December 13, without glycosuria. Bread feeding on December 15 brought out a heavy glycosuria, which did not disappear when meat diet was resumed on December 20. The subsequent course was that of diabetes gravis. It is not certain that the carbohydrate feeding was of any great importance in this case.

Dog 38; female; age 2 years; weight 5370 g.

August 2, removal of pancreatic tissue weighing 13.7 g. Remnant communicating with main duct estimated at 2 g. (about ⅛).

A more accurate condition of balance resulted than I have seen in any other animal except Dog 154; for it was possible to produce or suppress glycosuria according as larger or smaller quantities of *meat* were fed. Thus the feeding of 200 g. meat on August

5 caused no glycosuria, but 400 g. on each of the two following days caused considerable glycosuria. Again, on August 10 and 11, a certain quantity of meat was endured, but when the "dose" of 250 g. beef was reached on August 12, a slight glycosuria began. Such a condition is of course too delicate to last, and it promptly disappeared, so that on August 16, even 500 g. meat caused no glycosuria. A day of bread-feeding did not bring back the intolerance of meat. The succeeding days showed continued freedom from glycosuria on meat diet, and on August 22 a subcutaneous injection of 3 g. dextrose per kilo was assimilated without glycosuria. But since the tendency to glycosuria was so evident just after operation, there is a question whether this animal does not furnish a control for Dog 20. Carbohydrate feeding shortly after operation resulted in diabetes gravis in Dog 20. Dietetic rest after operation resulted in the development of a certain degree of tolerance in Dog 38. There is no doubt that in the few days following operation, conditions are more labile than they are thereafter. It is possible that a very brief period of overstrain of the assimilation at this time may turn the scale. On the other hand, sparing the assimilative power may perhaps give a chance for successful organic or functional hypertrophy of the pancreatic remnant.

Twenty-two days after operation (August 24), bread feeding was begun, and a high glycosuria thus maintained. But return to meat diet, August 31 to September 12, showed that diabetes gravis was still absent.

On September 12, bread feeding was again instituted, and on September 14, in the midst of the glycosuria, a bit of pancreatic tissue was removed, weighing 0.5 g. This operation revealed the usual reason for the previous gain in tolerance, viz., hypertrophy of the original remnant. Later, at autopsy, the remnant was found to weigh 3 g.

The result of this secondary operation was heavy glycosuria, first on bread diet, then on meat. Permanent diabetes gravis was in fact the outcome. A question is still possible whether the result was due entirely to the slight operation on the pancreas, or whether the diet was a factor.

Dog 89; male; adult; weight 7425 g.

September 17, removal of pancreatic tissue weighing 13.7 g. Remnant communicating with main duct estimated at 1.2 g.

End of processus uncinatus transplanted subcutaneously also estimated at 1.2 g. The two remnants together made up a trifle more than one-seventh of the pancreas.

No diabetes resulted from the operation. Bread-feeding resulted in a high percentage of glycosuria on September 25, but not again, except for a small showing on September 29.

On October 4 the subcutaneous graft was removed by a very easy operation, the dog suffering no disturbance except from the brief anæsthetic. Diabetes gravis did not result. The pancreas remnant still present was, according to the estimate at operation, not much more than one-fourteenth of the gland. If this alone had been left at the original operation, diabetes gravis would inevitably have resulted. Its failure to occur in this instance might mean one of two things; either the trauma of operation is one factor in the production of diabetes, or else changes occurred in the graft since the original operation. In a later chapter, the former of these possibilities will be ruled out. Operative trauma is not a determining factor in the production of diabetes, and the absence of diabetes in this case is not due to the fact that removal of a subcutaneous graft involves less nervous and circulatory disturbance than a primary pancreatic operation. The second possibility, viz., that time had enabled the remnant to undergo compensatory change, is therefore the correct explanation. It is further supported by the finding that the subcutaneous graft, estimated originally at 1.2 g., weighed when removed 3.3 g. The duodenal remnant itself was originally estimated at 1.2 g. Later, 0.5 g. of tissue was removed from it, and still its weight at autopsy was found to be 1.75 g. In other words, it nearly doubled in size.

After removal of the subcutaneous graft, feeding of bread and glucose was begun on October 6. Heavy glycosuria was thus easily maintained. On October 9, the diet was changed to meat. Glycosuria persisted, but its course is typical; 4.9 per cent, 1.6 per cent, 0.9 per cent. Such a decline is infallible evidence of transient diabetes gravis; on continued meat diet the glycosuria would promptly have ended. Bread-feeding was therefore resumed, with resulting heavy glycosuria.

On October 25, the diet was changed to meat, and glycosuria instantly ceased. In other words, after all this glycosuria, the tolerance was really better than on October 10–12.

Bread-feeding was therefore resumed, and in the midst of the glycosuria, on October 30, a trifle of tissue (0.5 g.) was removed

from the pancreas remnant. As in practically all my operations, post-operative glycosuria was absent; no urine was passed till November 1, and it was negative. Carbohydrate feeding on November 1 and 2 brought out heavy glycosuria, which persisted on meat feeding. Diabetes gravis was permanent, and ran the usual course. The final carbohydrate feeding had been so brief that its influence was probably not great.

In other experiments, I have tried feeding dextrose and injecting dextrose within the first hours and days following operation, and nothing has been gained except as already indicated; viz., if a dog is diabetic, the sugar may send him down-hill, but it cannot make him diabetic if he is not already so. It will be noted that Dog 20 received a large dose of dextrose on the evening *before* operation, and that diabetes resulted with a rather large remnant of pancreas. As usual, the post-operative urine was sugar-free. According to my experience, this preliminary sugar-feeding is without special influence, but I have not given it a very thorough trial.

A further question is possible regarding the influence of food given prior to operation. The character of such food, whether carbohydrate or other, may be less important than the act of digestion itself. As mentioned elsewhere, important relations exist between the internal and external functions of the pancreas. Moreover, the mere shock to the pancreas of operation under these conditions may perhaps be greater than in the fasting state. In such an operation, one finds the stomach and duodenum full of food, the chyle-vessels shining white, and the pancreas turgid with blood. The inconvenience is much greater, especially because the digesting pancreas bleeds so freely. In a series of experiments, I have found that there are no important differences in the results, whether the operation is performed upon the digesting or upon the resting pancreas. If any such differences exist at all, they are within very narrow limits. Two illustrations may be presented as typical.

Dog 170; male; age 2 years; weight 9675 g.

December 14, removal of pancreatic tissue weighing 19 g. Remnant communicating with main duct estimated at 2.6 g. The dog was fed heavily with bread-and-meat mixture on the evening before operation, and had feed in the cage at the time of operation.

Active digestion was found in progress. The remnant was between an eighth and a ninth of the gland, yet glycosuria appeared very promptly and was unusually severe. Distemper caused loss of appetite, yet this intense glycosuria continued. The case proves nothing, for a few other dogs with even larger remnants have shown very severe diabetes, even though they had not been fed before operation.

Dog 169; male; age 1 year; weight 9250 g.

On December 13 was fed an excess of bread-and-meat mixture. On December 14, partial pancreatectomy was performed at the height of pancreatic digestion. The tissue removed weighed 21.8 g. The remnant, communicating with the main duct, was estimated at 4.6 g., *i.e.*, $\frac{1}{6}$ of the gland. Sugar was absent both in the post-operative urine and thereafter. The dog was able to live on bread without glycosuria. The behavior was therefore precisely the same as when this same proportion of pancreas-tissue is removed from a fasting dog.

Conclusions and Remarks.

A number of points noted in passing require no further comment. As stated, a considerable number of dogs would be necessary to establish the main point beyond question, and the experiments would require a number of months. The dogs in question must represent a border-line condition, which by practice is not difficult to obtain.

Attention may be called to transient diabetes levis. This is an absolute term. The dogs at the outset are genuinely diabetic, yet they recover in spite of the heaviest carbohydrate diet and the most intense glycosuria. After this glycosuria has ceased, the animals are no longer diabetic; they react negatively to the tests for diabetes, though their sugar-tolerance is low; and apparently it is not possible by any diet continued for any length of time to make them diabetic. Starvation brings a return of alimentary glycosuria, but it is not permanent. In other words, no matter how low the carbohydrate tolerance, sugar can never produce diabetes in a non-diabetic animal. The recovery from the diabetes is apparently the result of marked hypertrophy of the pancreas-remnant. Diabetes, which cannot be produced by diet, results very easily from the removal of a very small amount of pancreatic tissue.

There is a question whether a condition which is no more than diabetes levis at the outset ever becomes permanent. That is, if after operation the dog is free from glycosuria except when fed carbohydrate, this glycosuria generally, perhaps always, ceases with time. When it is to be permanent, the condition at first is generally or always diabetes gravis; *i.e.*, for at least a few days following operation, there is glycosuria on meat diet. This passes off, but leaves a permanent diabetes levis. Fully decisive experiments have not yet been performed, but my opinion is that both transient diabetes gravis and permanent diabetes levis are relative terms, and that Thiroloix and Jacob are correct in stating that the simple continuance of carbohydrate diet is sufficient to transform the light into the severe form. The point is an exceedingly important one; for these animals are free from hereditary taint or any predisposition of the nervous system, and the fact, if conclusively demonstrated, will show that sugar by itself is able to reduce the assimilative power, when the nervous system and the remaining pancreatic tissue are healthy. But this result can occur only when diabetes already exists. The result is not invariable, for, as mentioned, diabetes levis may prove transient in spite of diet. But in a certain class of cases, it is probable that sugar will show the same power of aggravating the diabetes as in the clinical disease. The following points still await a conclusive demonstration.

1. Whether transient diabetes levis is really an absolute term. It has proved so in my relatively few and brief experiments. But a question is still possible whether there has been a definitive recovery from the diabetes. By suitable under-nutrition, Hofmeister was able to keep up a slight glycosuria in normal dogs for considerable periods. Starvation brings back the glycosuria *ex amylo* in the dogs referred to, and by prolonged under-nutrition on carbohydrate-rich and protein-poor diet, especially with some sugar in it, it would very likely be possible to maintain glycosuria for a considerable time. It is possible that months of such treatment might bring out a true and permanent diabetes in these animals.

This does not mean that malnutrition has any specific influence. It merely means that the functions of the pancreas suffer like those of other organs.

2. Whether carbohydrate feeding hastens very materially the downward course of dogs with permanent diabetes levis. A certain

degree of such hastening is to be assumed. But it is very important to know how the carbohydrate-fed dogs compare with similar dogs fed constantly on meat. Are the latter animals able to live out their natural life-times without diabetes? Does the lowering of tolerance to the point of glycosuria *ex amylo* persist throughout life? An affirmative answer is probable for this last question. Also, the ill effects of continued carbohydrate diet will probably prove to be very marked. But as yet, these important questions await a conclusive answer. They are of special theoretical importance, because it seems probable that we have here the first positively demonstrable example of the breaking down of an internal function by over-strain. It is important to emphasize that this loss of internal function occurs when atrophy of the pancreas-remnant (such as brings on Sandmeyer diabetes after ligation of the ducts) is absent, and while this remnant continues to perform actively its function of external secretion.

The direct relations of these experiments to the facts and theories of clinical conditions are also important. Three such relations are worthy of special note.

1. They are of some interest in connection with traumatic glycosuria and transitory diabetes in man. Reports are received from time to time of patients whose condition can properly be interpreted only as diabetes, but who yet recovered. Some such reports will be reviewed in Chapter XVIII. In such cases, the physician feels that he assists the patient by placing him on carbohydrate-free diet. Other patients have recovered in spite of mixed diet. The conditions have their analogy in dogs. Some dogs shortly after operation show transient diabetes levis; their tolerance soon increases, no matter what they eat; no diet can make them diabetic. But there are these other animals on the border-line; furthermore, there is evidence that carbohydrate diet is far more injurious just after the pancreas-operation than later. Not every nervous glycosuria in man need be considered diabetic; in some of them, the nerve-supply of only the liver, not the pancreas, may be involved. Tests of the dextrose paradox and diuresis can decide, though it is better not to make such tests in such cases. But physicians are justified in thinking that prescription of carbohydrate-free diet is proper in traumatic glycosuria, and that patients may sometimes be saved from diabetes thereby.

2. These results throw experimental light upon the incidence

and geographical distribution of diabetes, mentioned in Chapter III. Dogs which have lost a certain amount of pancreatic tissue will become diabetic irrespective of diet. Dogs which retain a sufficient amount of pancreatic tissue will never become diabetic, irrespective of diet. But between these two groups is an intermediate group. On an Eskimo diet they may be found to live in health. On a Hindu diet they soon go down into fatal diabetes. The sugar of the latter diet probably over-stimulates a pancreatic function through its nervous mechanism. The proportion of predisposed persons susceptible to this influence is considerable. The nervous system is a factor, as well as the sugar. Heredity, the general health, and many contributing influences cannot be ignored. Our civilization has brought increasing nerve-strain, sedentery life, and sugar consumption. An increased incidence of diabetes is therefore to be expected. In countries or among races where the above factors are prominent, most predisposed persons will die of diabetes. Individuals with similar nervous predisposition among the Eskimos might live out a natural lifetime, or the diathesis in them might conceivably be manifested in some other form, *e.g.*, Bright's disease. Other influences governing the incidence of diabetes should not be ignored, but the influence of carbohydrate diet may be considered to be experimentally demonstrable. This influence is never to produce, but only to aggravate, diabetic tendencies.

3. These experiments have a bearing upon the doctrine that the obesity sometimes preceding or accompanying diabetes is caused by hyperglycemia. In Chapter III it was pointed out that this doctrine has no experimental basis, and it was shown by experiments with subcutaneous injections of dextrose in full-fed animals that hyperglycemia does not necessitate fat-storage. In Chapter VII, it was pointed out that to attribute the obesity to hyperglycemia is improbable and superfluous. There is sufficient evidence to show that obesity is frequently an accompaniment of disorders of internal secretion, irrespective of hyperglycemia. The above hypothesis assumes a specific disorder of fat metabolism in some cases, and this is sufficient without the hyperglycemia. It is now evident that dogs with diabetes levis furnish the conclusive experimental proof of the non-production of obesity by hyperglycemia. The diabetes may be of any grade desired; by means of diet also it is possible to determine whether the hyperglycemia shall be slight or intense. These animals with diabetes

levis are well and strong, lively and happy; they can gain weight and even grow decidedly fat, but never any fatter than other dogs. The constant hyperglycemia never leads to pathological obesity, in experiments extending over weeks and months. The demonstration, therefore, that these dogs are thoroughly capable of depositing fat, and yet the continual hyperglycemia causes no abnormal fat-deposit, constitutes the proof once for all that fat-formation is not the result of mere excess of dextrose in the blood. The idea that the fat-cells retain the power of using dextrose, more tenaciously than other cells, is experimentally untenable. The hypothesis of "diabetogenous obesity" should be abandoned.

CHAPTER XIV.

ACIDOSIS.

Acidosis signifies an abnormal content of acid substances in the blood and tissues. It ordinarily has reference to the well-known "acetone bodies," but experimentally attempts to imitate the condition have been made with various acids. There is a slight distinction between acidosis and ketonuria, the latter of which denotes the presence of acetone, diacetic, or β-oxybutyric acid in the urine. The subject is touched only casually here, in connection with incidental observations in animals with the type of diabetes described heretofore, and also a series of experiments concerning the production of glycosuria, and the question whether diabetes may be a primary acidosis. A few references may be reviewed, in three divisions.

1. Clinical acidosis.
2. Experimental acidosis.
3. Acid bodies in relation with glycosuria.

1. Clinical Acidosis.

An excretion of acetone bodies is normal, to the extent, on mixed diet, of 1–3 centigrams per day through the kidneys, and about 3–8 milligrams through the lungs. Though the excreted substance has long been referred to as acetone, Embden and co-workers have shown that little if any of it is eliminated as preformed acetone. The other two "acetone bodies" are the ones which occur in the blood and tissues; especially, β-oxybutyric acid circulates in excess in diabetes. In acidosis, according to several researches [see Gigon (2)], there is a fixed proportion between the quantities of acetone and β-oxybutyric acid excreted, the proportion varying with different patients but being constant for the same patient. Carbohydrates are excluded as a source of the acetone bodies. Formation from protein is possible. The principal origin is considered to be from fat. Contrary to previous opinions, Forssner has proved that ingestion of fat increases slightly the excretion of acetone bodies. Therefore the reasoning

that fat-ingestion cannot increase the formation of acetone bodies because it does not increase the utilization of fat is to this extent incorrect. Forssner considers two possibilities, either that the food-fat behaves differently from body-fat in metabolism, or that the processes which make the food-fat assimilable transform a portion of it into acetone; he deems the latter more probable. These observations were made by Forssner upon himself on carbohydrate-free diet. Von Noorden [(1), p. 141] accepts the correctness of the observations, but interprets them on the basis that the organism was unaccustomed to withdrawal of carbohydrate. According to von Noorden's experiments with mild diabetics, a longer continuance of the carbohydrate-free diet trains the body to keep up its glycogen stores from non-carbohydrates, and then fat-feeding does not produce even the small increase of ketonuria observed by Forssner. Fat-feeding is not to be feared in diabetes.

An increase of excretion of acetone bodies above the normal is a relatively common condition. Fasting produces it, or in man a simple insufficiency of carbohydrate, and it is found in numerous patients with malnutrition — fever, cachexia (including cancer), intestinal diseases, etc. Magnus-Levy (1) states his experience that the smell of acetone can be perceived in almost every tenth patient entering hospital. Porges (6) has described acidosis in a wide variety of clinical conditions. Young children are especially easily subject to acidosis. Ordinarily, the acidosis found in general diseases is not dangerous; the patients do not die of acidosis. In diabetes, as is well known, the acidosis may be intense and fatal. But the amount of acetone bodies excreted was formerly greatly over-estimated. Von Noorden now accepts 30–40 g. (expressed as β-oxybutyric acid) per day as the ordinary maximum in even the worst cases, and only very rarely is as much as 55–60 g. daily eliminated. There are two theories seeking to explain the diabetic acidosis; (*A*) diabetic acidosis is a condition sui generis; (*B*) diabetic acidosis is due solely to carbohydrate deficiency.

A. Diabetic Acidosis a Condition Sui Generis.

This has long been the prevalent view. Some authors, as mentioned in Chapter III, formerly attempted to bring it into relation with the hyperglycemia. Various other explanations have been more plausibly suggested, all of them regarding the acidosis as a special anomaly, peculiar either in kind or in degree

to diabetes. As evidence for this view may be mentioned the high content of acetone bodies in diabetic organs, the greater production of acetone bodies in diabetic as compared with normal livers, and the fact that diacetic and β-oxybutyric acids when ingested in moderate quantities (15–20 g.) by normal persons are burned almost completely, whereas in diabetes the ingestion of similar quantities increases the ketonuria. The clinical evidence in favor of this view was summarized by von Noorden [(3), p. 593 ff] as follows.

"1. There are diabetic patients who tolerate carbohydrate — at least, of certain kinds — so well, and absorb and oxidize so much (*e.g.*, 70 to 100 g. per diem), that if they were not diabetic no acetonuria would occur; and yet they excrete quite large quantities of acetone.

"2. Many diabetics respond to the change from mixed diet to one free from carbohydrate by developing marked ketonuria; the latter does not disappear when carbohydrate is again given. The prognosis is then very unfavorable.

"3. In other cases the ketonuria resulting from strict diet is temporary or absent, or falls considerably after an initial rise. This is quite different from the ketonuria of non-diabetics, and can only be explained by supposing that the removal of all carbohydrates improves the general condition, and alleviates the pathological condition which produces ketonuria. . . . Satta published a most instructive case from my wards. The patient, suffering from very severe diabetes, excreted 2.21 grams of acetone bodies (reckoned as oxybutyric acid) upon mixed diet. On the first two days of strict diet the average was 19.1 g. of acetone bodies and 141 g. of sugar. Very large quantities of fat, sesame oil, butter, ox fat, pig fat, 150 to 200 g. per diem, were given, and yet the ketonuria sank continuously, and on the eleventh to thirteenth days of strict dieting only 1.5 g. were eliminated, along with 114 g. of sugar; four days later the ketonuria had fallen to 0.8 g.

"4. In different phases of the disease, even when the diet and the amount of sugar katabolized are approximately constant, the ketonuria may show wide variations. . . . Two diabetic patients, both bodily strong, and of approximately the same weights (65 and 67 kilograms), had been having the same diet with restricted carbohydrates (250 g. of meat, together with eggs, cheese, butter, and green vegetables) for ten days. Both were as nearly as possible in nitrogenous equilibrium, and the urine, under the strict régime, was free from sugar. They were both living under exactly the same external conditions, and were metabolizing the same quantities, not only of protein and carbohydrate, but also of fat. On the four following days successively the one excreted 25 g. of acetone bodies in his urine, the other 1.2 g., reckoned as oxybutyric acid in each case."

B. Diabetic Acidosis Due Solely to Carbohydrate Deficiency.

This, the now more generally accepted view, was first strongly supported by the work of Landergren, and after him Forssner and others. These two authors in particular have shown that

by suitable restriction of diet, the ketonuria of normal persons can be made to attain a height comparable to that of the diabetic, and that dangerous symptoms may result from this acidosis. In one of the experiments upon himself, Forssner observed an excretion of acetone substances on one day as high as 42.8 g. Also, the acidosis may continue when, like the diabetic, the normal subject ingests a small daily ration of carbohydrate; *e.g.*, excretion of as high as 32.3 g. acetone substances when the diet included 40 g. carbohydrate. Different non-diabetic persons show just as wide variations with respect to acidosis as different diabetics; the cause of these individual differences is unknown. The perfusion experiments of Embden and co-workers agree well with the above view. Embden and Michaud proved that the liver and muscles of depancreatized dogs destroy diacetic acid as actively as normal. Also, an increased formation of acetone bodies was demonstrated by Embden and Lattes not only in the livers of depancreatized dogs but also in the livers of phloridzinized dogs. Since it is possible to distinguish sharply between diabetes and phloridzin glycosuria, it becomes evident that the increased acetone-body formation is not peculiar to diabetes, but is shared by it with another condition, with which there is probably nothing in common except the deficiency of carbohydrate. The better accepted opinion on this subject at present is that of Landergren, "The acidosis of the diabetic is absolutely physiological."

The fundamental cause of acidosis, the reason why it occurs when there is lack of carbohydrate and is abolished by carbohydrate, is as yet not determined. Gigon (2), after an admirable review of the subject, names the following possibilities.

1. Acidosis may be a direct sequel of carbohydrate deficiency. (Geelmuyden's first hypothesis, that the acetone bodies undergo a synthesis with carbohydrate. Later theories that the combustion of carbohydrate is necessary for the combustion of fat or of acetone bodies. "Fat burns in the fire of carbohydrate.")

2. Acidosis is the consequence of increased utilization of fat.

3. Acidosis stands in relation with the formation of sugar from protein (Landergren).

4. The acetone bodies result from the formation of sugar from fat (v. Noorden).

The suggestion of Allard, that acidosis is a complication of diabetes, due to some special process, perhaps in the liver, is hardly admissible at the present time. As a fifth possibility may,

however, be mentioned the suggestion of Pribram, who on the basis of perfusion experiments of normal and phloridzin livers with β-oxybutyric acid, thinks that the normal disposal of this acid may be a synthesis, not a breaking down, and that the liver which has lost the synthetic power may attempt to dispose of the acid by oxidation. His experiments touch the unsettled question whether only one, or more, acetone bodies are formed normally in intermediate metabolism.

2. Experimental Acidosis.

Experimental acidosis is of (*A*) diabetic and (*B*) non-diabetic type.

A. Experimental Diabetic Acidosis.

Acidosis was observed by the first workers with experimental diabetes. Minkowski [(1), p. 97] reported that five of his series of animals excreted large quantities of acetone, diacetic, and β-oxybutyric acid. The elimination sometimes began only in the later stages of the disease, and was always moderate. As in human diabetes, it was independent of the degree of glycosuria. By feeding of oxybutyric acid it was proved that the dogs were still able to burn this substance.

Sandmeyer (2) observed slight acidosis in his dogs with chronic diabetes, generally amounting only to a faint acetone reaction in the urine. In totally depancreatized dogs he had failed to find a trace of ketonuria.

Baer (1 and 2) studied the susceptibility of different species to acidosis. His first paper shows that a phloridzinized dog is free from acidosis so long as he is in nitrogenous equilibrium. Ketonuria appears on starvation. Sugar prevents it, and it likewise disappears as soon as food restores the animal's nitrogen balance. Baer (2) proved that all animals except the rabbit are able to respond to "acid" diet with increased ammonia production. Man and monkey show acidosis on mere withdrawal of carbohydrate, the pig only on complete fasting, and other species only after considerable nitrogen loss, or with phloridzin poisoning. Geelmuyden and Voit (ref. by Hammarsten) noted other differences between dog and man; in dogs the excretion of acetone bodies is not increased but diminished in starvation; it is increased by increased ingestion of meat, and is not diminished by carbohydrates. It is well recognized that carnivorous animals are able

to utilize protein for their carbohydrate needs far better than man. Man possesses this power to some extent; increase of protein in the diet of human beings with acidosis may diminish the ketonuria [Magnus-Levy (4), p. 172].

Brugsch took the position that extreme acidosis never occurs in diabetic dogs; that they invariably die of inanition and not, like human diabetics, in coma. Experiments of Brugsch and Bamberg supported this view. The importance attached to it is shown by the following quotation from Brugsch (1). "This difference is the most fundamental difference between pancreas-diabetes and the severe form of diabetes in man. Hence the conclusion is that pancreas-diabetes means simply and solely a disturbance of carbohydrate metabolism, therefore is a pure glycosuria. Therefore if we find a diabetes mellitus, especially the severe type, combined with pronounced acidosis, this finding speaks, according to our experience thus far, . . . against a pancreas-diabetes."

Allard (3), with the support of Minkowski (6), opposed this opinion. He states that acidosis is not such a great rarity in dogs, provided no fragment of pancreatic tissue remains; and he presents records of dogs with high acidosis, involving excretion of acetone, diacetic and oxybutyric acid to the amount of several grams daily. He reports a few cases of death of diabetic dogs in coma. Though dogs vary as respects acidosis, so also do human patients. Allard considers the differences explainable on the basis of species, and looks upon acidosis as a complication, perhaps a disorder of the liver.

B. Experimental Non-Diabetic Acidosis.

Experiments with non-diabetic acidosis have mostly been performed in connection with the two principal theories which seek to explain diabetic coma: (I) the theory of simple acid poisoning; (II) the theory of specific intoxication.

I. Theory of Simple Acid Poisoning.

Walter in 1877 proved that rabbits poisoned by intrastomachal injection of suitable doses of hydrochloric acid die in a condition of collapse and unconsciousness, with dyspnea resembling the Kussmaul diabetic type. The impoverishment of the tissues in alkali is indicated by the increased ammonia excretion. A rabbit

which receives a sufficient dose of sodium bicarbonate subcutaneously is able to endure three times the fatal dose of acid by stomach without symptoms. When an animal which has received a fatal dose of acid is practically dead, with heart and respiration both stopped, an intravenous injection of alkali restores it to life and well-being.

Stadelmann, a pupil of Naunyn, in 1883 founded the theory of acid-poisoning as the cause of coma and increased ammonia excretion in diabetes, and inaugurated the treatment of acidosis by means of alkali. He referred to Walter's experiments for support. This treatment has proved itself one of the most brilliant things in diabetic therapy. Diabetics still die in coma, and only a minority are saved by alkali when coma has actually supervened; but some patients are thus saved, and in a far larger number, coma is prevented or postponed by prophylactic use of alkali. Naunyn claims the change to strict diet has never resulted in acidosis since he adopted the routine of giving sodium bicarbonate at the same time. The name acidosis, given by Naunyn, connotes the etiology of coma in a simple acid poisoning.

A review of the arguments in support of the simple acid-intoxication theory is presented by Magnus-Levy (1). He testifies to three patients whom he saw in actual coma saved by alkali treatment. He ascribes the general failure of this therapy in coma to the large quantities of acetone bodies which are constantly being formed, so that the amount of alkali introduced does not suffice to neutralize them. He has himself found 100 to 200 grams of oxybutyric acid in the bodies of patients who have died in coma. This portion of the acid, which remains in the body, is what kills the patient. The portion found in the urine is without significance; it can no longer harm the patient, and it may actually be found diminished in coma, because the weakness and intoxication prevent its elimination.

II. Theory of Specific Intoxication.

Klemperer in 1889 argued for the view that coma is not the result of acid poisoning, but that coma and acidosis are both results of a common cause, viz., poisoning by unknown toxic substances. His extreme position is summed up in his statement, "The diabetic does not go into coma because his blood becomes acid, but his blood becomes acid because he becomes comatose."

Long search has been made and is still being made for the specific poisonous substances. Sternberg in 1899, assuming that β-amido-butyric acid is the mother-substance of β-oxybutyric acid, performed experiments to show the toxicity of the former substance, and proposed it as the specific cause of diabetic coma. Grube (1) confirmed Sternberg's findings. He agreed that injection of β-amido-butyric acid in cats produces a condition resembling diabetic coma, and he succeeded also (where Sternberg had failed) in obtaining some positive reactions of acetone and diacetic acid in the urine. Solution of 2 per cent sodium carbonate injected subcutaneously or intravenously had a powerful effect in neutralizing the poison. Sugar was found sometimes in the urine, but was attributed to the manipulations, since cats so readily show glycosuria under such conditions. The Sternberg hypothesis has since been dropped.

Acetone is not highly toxic. Albertoni and Pisenti [ref. by Naunyn, p. 338] found that rabbits endure 6 g. acetone by mouth daily for 22 days without symptoms of intoxication. Kussmaul [ref. Naunyn, l.c.] obtained symptoms of drunkenness in these animals only when he gave as much as 5 g. within two hours subcutaneously. In dogs 10 g. acetone subcutaneously was without effect, and in man 6 g. per day could be given without ill effect. Rörig [Diss. Würzburg, 1898; ref. by Lepine (1), p. 540] also found that 6 g. of acetone can be ingested by a 60 kilo person without symptoms. A dose of 12 g. causes slight symptoms of drunkenness. Frerichs [ref. by Lepine, l.c.] gave healthy persons as much as 40 g. acetone without result except acetonuria and an aromatic odor of the breath. Ingestion of 10 grams β-oxybutyric acid was without effect. But Waldvogel saw hemorrhagic nephritis in a rabbit after subcutaneous injection of a gram of this acid.

Desgrez and Saggio found the following doses necessary to kill a rabbit by intravenous injection:

Acetone	4.35 g. per kilo
Diacetic acid	2.17 g. per kilo
β-oxybutyric acid	1.59 g. per kilo
Butyric acid	0.329 g. per kilo

These authors also gave daily subcutaneous injections of small doses of each of the three acetone bodies in guinea-pigs for two months, with practically no effect except a diminution of the quantity of urine.

Lepine [(1), p. 581 ff] reckons that since Walter found 0.9 g. per kilo to be the fatal dose of HCl for rabbits, the fatal dose of β-oxybutyric acid on the basis of pure acidity should be 2.6 g. per kilo. But Desgrez and Saggio found the fatal dose to be actually 1.6 g. per kilo. Therefore β-oxybutyric acid must be poisonous by virtue of special properties in addition to its acidity.

Herter and Wilbur [ref. by von Noorden (1), p. 148] proved experimentally that oxybutyric acid has a toxicity out of proportion to its mere acidity. The neutral sodium salt of this acid was also found to be poisonous.

Marx in 1910 experimented with the effects of sodium butyrate in puppies. He claimed that this substance causes typical coma when given intraperitoneally, but not when given by mouth. His conclusion is that it and its products (acetone, etc.) produce coma by a specific poisoning rather than by a simple acid-intoxication.

Ehrmann, Esser, and Loewy in a trio of collaborative researches in 1911 proved the toxicity of sodium butyrate given in feebly alkaline solution either orally or intravenously in dogs. They produced by either route a condition resembling diabetic coma, with excretion of only very small quantities of acetone bodies in the urine. This coma is not a simple acidosis, but a specific poisoning by butyric acid.

Salomon [ref. by von Noorden (1), p. 149] has demonstrated a certain degree of toxicity also for salts of diacetic acid.

Naunyn (p. 344) admits that patients in coma are seldom saved by alkali injections. Improvement may be "magical" in some cases, but even so, the patients die 24 hours or so later. He does not claim that results of this temporary character prove the specificity of the bicarbonate treatment. The stimulating or diuretic effect of the injection may be the cause. He refers to the report of Hilton-Fagge in 1874 of a similar magic cure of diabetic coma by intravenous infusion of a mixture of sodium chlorate and sodium phosphate, *i.e.*, an *acid* solution. This "cure" lasted three days. Likewise, Young postponed death for eleven days by venesection followed by infusion of plain saline.

The supporters of the pure acid-poisoning theory explain the relative failure of the alkali treatment by the large quantities of acid bodies to be neutralized. This is the argument of Magnus-Levy (1); and Naunyn (pp. 344–5) calculates that there may be 200–300 g. β-oxybutyric acid in the body of a diabetic, requiring

160–240 g. sodium bicarbonate for its neutralization. Lepine [(1), p. 581], though he takes the opposing view, admits that he has given comatose patients 40 g. sodium bicarbonate at one dose intravenously, and the urine has always remained acid. The opponents of the pure acid-poisoning theory explain the benefits of the alkali treatment largely by the fact that it facilitates the excretion of the acetone bodies. Gigon (2) refers to the fact that the excretion of acetone bodies is not so enormous except in cases where much alkali is given; the alkali may increase not only the elimination but also the formation of acetone bodies. He refers to experiments of Henderson and Spiro, showing that in the acidity of the urine the organism possesses the power of protecting its stock of alkali; β-oxybutyric acid circulates in the blood combined with alkali as a salt, but it is excreted in the urine in large proportion (up to $\frac{2}{3}$) as free acid, and the base is retained in the body. Von Noorden [(1), p. 148] lays stress upon the fact that coma may be delayed by alkali, but it comes nevertheless; and he mentions cases in his own experience in which alkali was given for months in such quantity that the urine remained alkaline to death, yet death came from coma.

The striking positiveness of the experiments of the upholders of the acid-poisoning theory militates against their position. In the very moment of death, Walter's acid-poisoned rabbits could be completely restored by alkali. Aside from other arguments, von Noorden's observations of death in coma with alkaline urine seem fairly decisive. There may be an element of acid-poisoning in coma, but apparently it is not the most important feature. It appears more probable that some specific intoxication is present; but it is by no means certain whether this intoxication is caused by the well-known acetone bodies, or by other substances which are entirely unknown.

3. Acid Bodies in Relation with Glycosuria.

Pavy [ref. by Naunyn, p. 40] discovered that introduction of phosphoric acid intrastomachally or intravenously in dogs causes a slight excretion of sugar. He thus became the discoverer of acid glycosuria.

Goltz soon afterward proved that rabbits which received 10–12 cc. of 50 per cent lactic acid by stomach-tube showed glycosuria. This glycosuria did not appear till 36–48 hours after ingestion of

the acid, and was accompanied by albuminuria but not polyuria. If the doses were too large, no glycosuria occurred, because the animals did not live long enough.

Naunyn observed glycosuria in a dog poisoned with HCl, and Richter [ref. by Naunyn, p. 40] performed experiments with this type of glycosuria. Naunyn states that the glycosuria from acid poisoning occurs in only a minority of cases in either human or animal subjects. He attributes it to direct injury of the cells of the liver or pancreas, and compares it thus with the glycosuria obtained by Harley by injections of various irritant substances into the portal vein.

Külz (4) confirmed the occurrence of glycosuria in rabbits after intrastomachal injection of phosphoric acid. Glycosuria and albuminuria came on within two hours, and lasted two or three hours. Lactic acid, in greater dilution than employed by Goltz, likewise caused glycosuria and albuminuria within about two hours. Hydrochloric acid similarly produced glycosuria.

Frerichs [ref. by Lepine (1), p. 319] reported two cases of human sulphuric acid poisoning in which slight glycosuria was present, and a third in which glycuronic acid was present.

Kobert and Küssner [ref. by Lepine (1), p. 319] found in a series of cases of oxalic acid poisoning that the urine contained a reducing substance which was optically inactive. But Lepine, trying the question experimentally, found that a dog poisoned with sodium oxalate exhibited hyperglycemia and glycosuria, and that the reducing substance showed the rotation characteristic of dextrose.

Kleen (p. 52) cites authors who have witnessed glycosuria after poisoning with salicylic acid, prussic acid, orthonitrophenylpropionic acid, and the lower fatty acids.

Ruschhaupt in 1900 discovered that acetone causes glycosuria. He used rabbits, and gave the acetone sometimes orally, subcutaneously, or intravenously, but generally and preferably by inhalation. The glycosuria was slight, and generally disappeared in a few hours, but rarely persisted 1–3 days. Hyperglycemia accompanied the glycosuria. The sugar is derived from body-glycogen, for sufficiently prolonged fasting prevents or diminishes the glycosuria.

F. Müller continued the study, and concluded that acetone glycosuria is nothing specific, but depends essentially on asphyxia and cooling of the body.

The relation of acids to the economy of sugar and glycogen has given rise to some interesting researches. The inversion of polysaccharides by acids in vitro perhaps first suggested the idea. Gans in 1896 described the effects of alkali in inhibiting glycogen break-down. Experiments on the rate of oxidation of sugars in acid medium have been performed by A. P. Matthews, McGuigan (3), and Bunzel. The last author comes to the following conclusion. Sugars with cupric acetate in solution of N/2 acetic acid are oxidized with relative initial velocities represented as follows:

Lactose	1	Galactose	8.72
Maltose	1.15	Mannose	8.72
Glucose	5.71	Levulose	55.13

The readiness of oxidation of levulose in an acid medium might here be supposed to correspond to its readiness of oxidation in the diabetic organism.

Kleen (p. 52) has the following note concerning the influence of reaction.

"Acids cause saccharification of glycogen and starch, while alkalies do not. Coignard watered radishes, Martin-Damourette a vine, with alkaline water, and thus obtained a much smaller amount of sugar in the roots of the former and in the fruits of the latter, than by using ordinary water. Ehrlich found that frogs living in a solution of glucose stored a good deal of glycogen in their livers when sodium bicarbonate was added to the solution of glucose, but a comparatively small amount when acetic acid was added. Pavy assumes that sulphuric acid injected into the blood favors the transmutation of glycogen in the liver into sugar, but that injections of sodium bicarbonate favor its transmutation into something else. His opinion that the latter-named injections decrease the hepatic glycogen was not borne out by the experiments of Külz, which yielded exactly opposite results. In cases of severe diabetes with large quantities of [diacetic and β-oxybutyric] acids in the blood the hepatic glycogen is distinctly diminished [Frerichs, v. Mering and Minkowski, Stadelmann]. As a result of his experiments Külz reached the somewhat uncertain conclusion that dextronic acid, sugar acid, and mucous acid contribute to the formation of glycogen in the liver. This seemed certainly to be the case with the anhydrid of glycuronic acid, which is molecularly closely related to glucose. Even if all these weak acids should in some way contribute to the formation of glycogen in the liver, it can scarcely be doubted that stronger acids in the blood are decidedly antagonistic to such a result."

Pavy and Bywaters showed with respect to both invertase and diastase, that acids serve as activators of the inert zymogen.

Pavy and Godden (1) found that intravenous injection of 2 per cent sodium bicarbonate inhibits postmortem sugar forma-

ion in the liver of a chloroformed cat; but acid may then give rise to sugar-formation. When part of a liver is ligated off, and the rest perfused with carbonate solution, sugar formation occurs in the ligated part, but the perfused part shows no sugar. In the living cat, chloroform anæsthesia causes marked glycosuria, but this can be prevented or stopped by intravenous injection of sodium carbonate. The authors accordingly speak of "abnormal conversion of glycogen into sugar" by the action either of chloroform or of nervous stimuli, "attributable, there are grounds for suggesting, to acidosis development."

Funck (2) has formulated a theory of diabetes, considering the disease to be a primary acidosis. Acid intoxication is assumed as either the primary or a contributing cause ("Ursache oder Mit-Ursache"). Stoklasa's suggestion of the rôle of potassium salts in sugar-combustion is adopted, and the acids are supposed to interfere with potassium fixation.

Experiments.

The present investigation has included orientation experiments in many different directions, some of them not reported. In view of the little knowledge concerning the nature of diabetes, it was deemed advisable to try as many different lines as possible, and not always to confine the attempts to what seemed probable. The possibility was considered that diabetes might be a primary acidosis, though masked for a longer or shorter period; also that substances of acid nature might contribute to the production of diabetes. The idea is improbable for many reasons; and however interesting the experiments of Pavy and others with acid glycosuria may be, it must be remembered that the largest alkali-injections have had no special effect upon the glycosuria of diabetes. A group of these orientation experiments, with others more or less related, may be summarized here.

A. Administration of Various Substances.

Neutral Fat.

Fat is considered the principal source of the acetone bodies; some authors consider it a source of sugar. There is no way of feeding the body with fat and compelling the combustion of it, as we can do with dextrose. If it were possible, the results might be interesting. In Chapter IV were mentioned several subcutaneous

and intraperitoneal injections of cottonseed oil; absorption was too slow for any effect. In other attempts, emulsified fat, even with a trifle of bile and pancreatic juice, has been absorbed no better. Barbéra reported equally poor absorption when the fat was injected in the form of thoracic-duct chyle from a digesting dog. Perhaps the intravenous injection of such chyle would be the only feasible means of giving over-doses of fat. I have performed several intravenous injections of cottonseed oil, and found it borne better than expected. Rapid injection of course causes acute death from embolism. In one dog, non-diabetic after removal of $\frac{5}{6}$ of the pancreas, I injected 25 cc. sterile cottonseed oil into the saphenous vein,the duration of injection being one hour. During the latter part of the injection the dog was in coma, with slow but strong heart, and slow sighing respiration, later labored. Death occurred an hour after the end of injection, and autopsy showed oil globules in the heart-blood and lungs. Sugar, albumin, acetone, and diacetic acid remained absent from the urine. The coma is explainable by simple embolism.

Glycerin.

Prolonged subcutaneous injections were without glycosuric or other perceptible effect. The experiment with Cat 18 is described in Chapter III.

Oleic Acid.

The higher fatty acids are considered the direct precursors of the acetone bodies. Munk found them to be exceedingly toxic; doses of 0.11–0.13 g. oleic acid injected intravenously during a period of 30–45 minutes were sufficient to kill rabbits by heart-paralysis. Tallqvist and others [see Faust] have studied chronic oleic acid poisoning; the effect is an anæmia somewhat resembling the pernicious type. Oleic acid is absorbed more rapidly than cottonseed oil, apparently much more rapidly from the peritoneum than from the subcutis. In experiments with rats, weighing 150–200 g. each, I found that as much as 2 cc. oleic acid injected subcutaneously might cause no symptoms. In the peritoneum, injections up to $\frac{1}{2}$ cc. were endured safely; anything above that was fatal. There were no symptoms except weakness. Fat-crystals were found in the peritoneum at autopsy, and frequently small white dots like fat-necrosis. Glycosuria never occurred. A young cat weighing 1430 g. received 4 cc. oleic acid

into the peritoneum at 3.30 p.m. That evening, the animal appeared sick or semi-conscious, and death occurred some time after 10 p.m. Autopsy findings as in the rats; no glycosuria.

Sodium Oleate.

One rat and one guinea-pig received small subcutaneous injections (generally 5 cc. 1 per cent solution per kilo) of sodium oleate daily for a month. No symptoms.

Sodium Butyrate.

This substance is too irritating for subcutaneous use. One cat received several injections; there was no infection, but later, at the sites of injection, a slow induration followed by indolent ulceration. No other symptoms.

Butyric and Acetic Acids.

Results from several mouth feedings in guinea-pigs were negative as to glycosuria.

Acetone.

This was given to a series of cats and guinea-pigs by mouth and subcutaneously; there were a smaller number of inhalation experiments, using a cone as for ether. Acetone by any route may produce glycosuria, but it is always slight, and the urine is diminished. In animals given varying doses, up to the point of drunkenness or unconsciousness, daily for a week, the glycosuria, instead of increasing, disappeared, obviously because the nutrition of the animals suffered. The tolerance of subcutaneously injected dextrose is lowered by simultaneous doses of acetone; but the paradoxical law still holds, and the urine is diminished.

Results with partially depancreatized animals are no different. An experiment of this kind was performed with Dog 74. The animal had diabetes levis, and during the days previously had been fed on bread-and-meat mixture in order to keep up a high glycosuria. In the midst of this glycosuria, on September 14, acetone was given by inhalation for $4\frac{1}{2}$ hours continuously, and for 4 more hours the dog was unconscious from the effects. The urine was much diminished, and contained albumin; but the sugar of the 24-hour specimen (September 15) was less than on the preceding days; and, owing to poor appetite, it became entirely negative on the following days. Acetone therefore has no diabetogenic effect in predisposed animals.

Alcohol.

Text-books assign to alcohol a rather definite position in the etiology of some cases of diabetes; reference is made to the frequency of the disease in certain wine-growing districts, among monks who manufacture liquors, among classes of the population who indulge in both sugar and alcohol, etc. Glycosuria is common after drinking "Swedish punch"; maltosuria may occur after beer-drinking; patients with acute alcoholism may show even glycosuria *ex amylo*. Explanations on the basis of an effect upon the pancreas have not been lacking. We have seen that dextrose is nearly all burned by the body, no matter how large a quantity is introduced. An interesting question arises when alcohol in large quantity is given simultaneously with dextrose, because, (1) alcohol is likewise a substance which the body is compelled to burn, and it is more easily oxidizable than sugar; (2) at the same time, alcohol poisons the body, including especially the nervous system, and possibly the organs which provide for dextrose metabolism. Granted therefore that alcohol lowers the dextrose tolerance, it is desirable to know whether this change is in the direction of diabetes.

Accordingly, a series of cats and guinea-pigs were treated with varying doses of alcohol, while at the same time they received dextrose either orally or subcutaneously. None of the experiments were longer than a week. Results were negative, irrespective whether the doses were small enough to affect the animal but little, or whether it was kept lying all day long in alcoholic stupor. No matter how much alcohol or how much dextrose was given, no suggestion of diabetes was encountered. Alcohol makes merely a reduction of the apparent tolerance of dextrose; the real tolerance is unaffected. Intoxicated animals continue to use nearly the whole of their dextrose injections, whether small or large. The paradoxical law is unbroken, and dextrose remains an anti-diuretic. Experiments of this type might be interesting in animals with transient diabetes levis, but none such were performed.

Ether.

Anæsthetics are related to the above-mentioned substances, and are known to cause glycosuria. It was desired to learn if this glycosuria bears any relation to diabetes. A few typical observations are as follows.

Dog 21 [see protocol in Appendix]. On March 16, this dog was subjected to emotional disturbance and also ether anæsthesia, in conjunction with an intravenous injection of 4 g. dextrose per kilo. There was no perceptible difference of utilization from other occasions when this or other dogs received the simple intravenous injection. Especially, the dextrose at first acted as a diuretic as usual, and then the secondary oliguria with continuance of glycosuria occurred as usual.

Dog 28, a mongrel female weighing 8 kilos, was found by tests to have a high dextrose tolerance of 9–10 g. per kilo. On a subsequent day, she received at 11:30 a.m., a subcutaneous injection of 9 g. dextrose per kilo. At 2 p.m. the urine was negative. From 2 to 3 p.m. she was kept deeply under ether, then returned to her cage. The urine was scanty as usual, and the glycosuria was only 0.9 per cent. The lowering of tolerance produced by ether is therefore insignificant, and the paradoxical law is not affected.

In several dogs depancreatized just short of diabetes, the effect of ether has been observed either purposely or in connection with various operations. The glycosuria has never been more than a fraction of one per cent, has never been accompanied by polyuria, and has shown no tendency to persist. A diabetogenic tendency of ether is therefore not demonstrable. Its effect even in predisposed animals is nothing but a slight, non-specific, toxic glycosuria.

Salts.

On the score of the supposed "acid intoxication" produced by salt injections (Schaps), also the NaCl glycosuria, and Stoklasa's notions concerning potassium, and the remote possibility of an ionic basis of diabetes, a series of salt injections were given. They were made subcutaneously, for the sake of more persistent effect, and because the intravenous method was not considered feasible for continued use. Cats and guinea-pigs received daily injections of isotonic or hypertonic solutions of the chlorides of sodium, potassium, calcium, and magnesium respectively, in increasing doses. After five weeks the attempt was abandoned. As noted in the next chapter, the apparent tolerance of a cat for dextrose is easily lowered by a simultaneous injection of salt or even cane sugar. But the effect is probably only upon the kidney, in the direction of diuresis and increased permeability. It is

present only for the time being; the prolonged treatment is without effect upon the utilization of dextrose.

Other Substances.

Series of daily injections were also performed with miscellaneous substances, viz., glycogen, dextrin, urea, Witte peptone, gelatin, and sterile egg-albumin. The injections were all subcutaneous, in guinea-pigs and rats. The longest duration was 3 or 4 weeks. There were no specific effects upon the sugar tolerance.

B. Acidosis in Diabetic Dogs.

The diabetes described in Chapter X is a new type of the experimental disease, and the behavior as respects acidosis is therefore of interest. Acidosis is of course absent except in diabetes gravis; and here, the cases fall roughly into two groups.

1. Cases in which cachexia is extreme and the fatal termination early, almost as after total pancreatectomy. In some of these the sweet odor of the urine has appeared early and lasted till death, with ketonuria such as characterizes the later stages of the more chronic cases.

2. In the typical cases of long chronic course, heavy acetonuria seems to be an invariable occurrence. The sequence is as in human diabetes, *i.e.*, at first absence of ketonuria, later a gradual onset, becoming heavier with time. In the later stages, the sweet odor may be most intense. The acetone excretion is very heavy; quantitative tests have not been made, but the ordinary reactions are positive in the urine, and heavy in the distillate; and when a 6–8 kilo dog is passing daily a litre or more of such urine, the output in proportion to body-weight must be considerable. A peculiarity is that the ferric chloride reaction has been uniformly negative. No special study of the subject has been made; but this test has been performed many times, with urines heavy with acetone. Whether β-oxybutyric acid is present cannot be stated, for this test has not been made.

The impression has been received that the onset of acidosis is hastened by anything that aggravates the diabetes. One means of aggravating the disease lies in subcutaneous dextrose injections. The suggestion is here ventured that though Underhill and Closson (3) found the urinary ammonia not increased

by subcutaneous dextrose injections in normal dogs, it is possible that the results in diabetic dogs may be found otherwise. Another influence aggravating the diabetes is starvation. During fasting, the output of sugar is of course less; but thereafter, the animal cannot build up its tissues like a normal dog. Its appetite is increased, and the more it eats the more sugar it eliminates and the worse the diabetes becomes. On the whole, it would seem that dogs with this type of diabetes offer interesting new opportunities for the study of acidosis. Whether the presence of a considerable mass of functionating pancreatic tissue has anything to do with the condition must be left for others to decide. It is noteworthy that Sandmeyer's dogs, with chronic diabetes after atrophy of the pancreas-remnant, showed nothing but slight traces of acetone; and Allard (3) laid it down as a necessary prerequisite for acidosis in dogs, that every trace of pancreatic tissue must be removed. As in regard to other things, so also in regard to acidosis, dogs such as I have described furnish a better reproduction of human diabetes than has heretofore been possible. The idea that acidosis constitutes a mark of distinction between human and "pancreatic" diabetes is shown to be unfounded. None of my typical animals have been allowed to die spontaneously. A few of them have been allowed to go to very late stages, when they were almost too weak to stand; and there has been no sign of impending coma. Notwithstanding the intense and prolonged acetonuria, it seemed evident that the animals would die of cachexia, without the slightest clinical sign of acidosis. The difference of species may explain this departure from the human conditions. But there is perhaps something more than this, as may be indicated by a comparative summary of the known facts, as follows.

1. Totally depancreatized dogs are generally free from ketonuria and coma.

2. A few totally depancreatized dogs may show marked ketonuria (acetone, diacetic, β-oxybutyric), and a still smaller number die in coma.

3. Dogs with Sandmeyer diabetes exhibit only slight ketonuria (acetone, diacetic) and die of inanition, not coma.

4. Dogs with the diabetes which I have studied excrete large quantities of acetone, but the urine gives no ferric chloride test. Death is from simple inanition, or at least, coma could possibly shorten life only by a few days, so far as my observations go.

5. Sternberg states on the basis of veterinary literature, that in the spontaneous diabetes of dogs, acidosis and death in coma are frequent.

An isolated observation, which seemed of interest from the standpoint of acidosis, was that concerning Dog 63. In this instance the partially depancreatized animal, free from glycosuria and ketonuria, was subjected to the Bernard puncture, and there was a prompt appearance not only of glycosuria but also of heavy acetonuria. The details are presented in Chapter XVII. Questions arise whether the cause of this sudden acetonuria was a sudden loss of glycogen, or a nervous stimulation to over-production of acetone bodies, or something else.

But after all, with due regard to all the interesting facts and possibilities concerning acidosis in dogs, it is doubtful if a fully satisfactory imitation of human conditions can be expected in these animals. The natural differences between the two species in regard to ketonuria, as mentioned earlier in this chapter, are so marked and so fundamental, that differences in regard to diabetic acidosis are to be expected. There is a question whether it may not be unsafe to base too many conclusions upon dogs or their organs, at least without controls chosen from other species. Clinically, dogs may show acidosis and according to report may occasionally die in coma, yet probably there is, generally or always, a considerable element of cachexia. The human condition — a patient in comparative well-being, rising ketonuria and ammonia excretion, prodromal drowsiness, perhaps a clearing up under alkali treatment, or perhaps the striking dead of an individual in a fair state of nutrition — such is not the rule in dogs. For a better reproduction of human acidosis we must turn to other animals, possibly the pig or rabbit, certainly the monkey. The practical certainty that diabetes can be produced by partial pancreatectomy in monkeys — a species naturally subject to the disease — was mentioned in Chapter X. It may even be that diabetes will result with larger pancreatic remnants than in dogs. At any rate, in these animals we may hope for a type of the disease which shall imitate satisfactorily the human condition, including acidosis. From studies of such animals we may hope for more light than heretofore obtainable concerning the problems of diabetic acidosis.

CHAPTER XV.

PHLORIDZIN.

PHLORIDZIN is a glucoside derived from the root-bark of the cherry, apple, pear, and plum. It can be split into glucose and phloretin. The latter is able to produce glycosuria, but in less degree than phloridzin itself. Phloretin in turn can be broken down into phloroglucin and phloretinic acid, which are without glycosuric effect.

Phloridzin produces glycosuria when introduced into the body by any channel. Its effect is quickest and greatest when given intravenously, still very great when given subcutaneously, and considerably less when given by mouth; the reason is that much of the glucoside is broken down in the intestine into products which are slow and difficult of absorption. Phloridzin is poorly soluble in water, though better in hot than in cold water. The solubility is greater in alkaline solution; 1 g. phloridzin will dissolve in 200 cc. of $2\frac{1}{2}$ per cent sodium carbonate solution [Lepine (1), p. 262]; but if injected *warm*, 1 g. can be given in 10 cc. 1 per cent carbonate solution [Loewi (4), p. 1187]; and this is the form in which it is generally administered intravenously. As phloridzin stands boiling, the solution is easy to sterilize. For subcutaneous dosage, the same solution can be employed, but an alcoholic solution is considered preferable; the effect in alcoholic solution is more prompt and intense. Phloridzin in substance may also be introduced under the skin. Cremer (1*A*) made a slit in the skin of frogs, inserted the powdered phloridzin, and sutured the wound. Coolen suspended the powder in olive oil, or in gum-arabic mucilage, and injected the suspension subcutaneously in dogs, obtaining thereby a glycosuria of varying duration, up to eleven days from one dose. By feeding phloridzin, von Mering occasionally obtained glycosuria for as long as three days from one dose. The duration of glycosuria when phloridzin solutions are injected intravenously or subcutaneously is shorter, varying with the dose. Glycosuria ceases as soon as the last of the phloridzin is excreted.

All species of laboratory animals are subject to phloridzin glycosuria. Dogs are most susceptible and most commonly used. Rabbits are slightly less susceptible. The condition has also been studied in the cat, goat, goose, hen, frog, etc.

The discussion of the effects of phloridzin may be taken up under three topics:

1. Pathological anatomy.
2. Pathological physiology.
3. Mechanism of glycosuria.

1. Pathological Anatomy.

In keeping with the relative harmlessness of phloridzin is the relative absence of anatomical changes from it.

Kolisch and Pineles described lesions of the blood-vessel walls caused by phloridzin, similar to the well-known changes produced by adrenalin.

Rosenfeld has done valuable work upon the fatty liver. The livers of normal fasting dogs contain only some 10–15 per cent fat. The livers of fasting phloridzinized dogs contain from 25 per cent to as high as 75 per cent fat. The fat disappears spontaneously when phloridzin is stopped. Also, the liver fails to become fatty if the animals receive sufficient food, either protein or carbohydrate; these foods not only prevent the fatty change, but also abolish it after it has occurred, even though phloridzin be still given. Rosenfeld has pointed out the opposition between fat and glycogen under these conditions; a glycogen-containing liver is not fatty; a fatty liver contains little or no glycogen. The actual processes governing the fatty deposit are unknown. By feeding dogs with mutton-fat till a store of this fat is laid up in their bodies, and then poisoning with phloridzin, it has been found that the fat of the liver is mutton-fat; *i.e.*, the fat has been carried into the liver from other organs, not formed in situ. Other organs do not show fatty changes from phloridzin.

With all its intense glycosuric action, phloridzin ordinarily produces no anatomical lesions whatsoever in the kidney. Trambusti and Nesti gave dogs daily doses of phloridzin, increasing from 0.1 to 0.5 g. per kilo, and sacrificed them on the fifteenth day. They found coagulation-necrosis of the convoluted tubules, and to less degree of the collecting tubules. Lepine [(1), p. 264] thinks their dogs must have been ill-nourished. Kossa (14) re-

ported albuminuria and cylindruria from phloridzin in rabbits. Seelig injected rabbits daily with 1 g. phloridzin subcutaneously for a month. The kidneys were found healthy except for necrosis of the convoluted tubules. Traces of albumin had been present along with sugar in the urine during treatment. Hartogh and Schumm reported parenchymatous nephritis with renal hemorrhages and fatty degeneration in their phloridzinized dogs. Policard and Garnier by massive doses of phloridzin in white rats produced renal lesions which they claim to be characteristic, viz., a "vitreous" degeneration limited strictly to the striate-bordered epithelium of the convoluted tubules. Fichera described deposits of glycogen in the cells of Henle's loops and the straight tubules, analogous to the changes described by Ebstein and by Ehrlich. Pari (3) found both the liver and the kidneys stained in abnormal manner by carmine injected intravenously in phloridzin-poisoned animals. Allowing for all the claims of all authors concerning renal lesions, the fact remains that the kidneys of phloridzinized animals are generally found absolutely normal. Loewi (4) has injected dogs daily for months, and found neither albumin, casts nor microscopic alterations.

Anything associated with glycosuria is certain to call up thoughts of the pancreas. Ghedini described pathological changes in the acini and diminished size of the islands of Langerhans in dogs after repeated doses of phloridzin, with a reduction of the entire organ even to $\frac{1}{2}$–$\frac{1}{3}$ the normal size. Vigliani failed to find such changes. The results of J. Lepine were also negative. Lazarus in 1907 fed guinea-pigs with phloridzin for long periods, in one instance for eight months. He reported the opposite change, viz., gigantism of the islands of Langerhans. Heiberg (3*A*), Tiberti (3), Frugoni and Stradiotti (1, 2, 3), and van Leersum and Polenaar proved that no such results occur, but that giant islets are a normal feature of the guinea-pig pancreas. Herxheimer likewise obtained negative results, and the same was true in the recent careful work of Cecil (4). We now know positively that the most prolonged treatment with phloridzin, either orally or subcutaneously, causes no pancreatic alterations whatever, and the dose necessary for glycosuria is neither greater nor smaller at the end than at the beginning.

2. Pathological Physiology.

This topic may be conveniently treated in the following subdivisions:

A. Carbohydrate metabolism.
B. Fat metabolism.
C. Protein metabolism.
D. General metabolism and diuresis.
E. Fate of phloridzin itself.

A. Carbohydrate Metabolism.

Phloridzin gives rise to one of the most intense of known forms of glycosuria. Moritz and Prausnitz reported sugar-excretion as high as 13 per cent. Von Mering, the discoverer of phloridzin glycosuria as well as of pancreatic diabetes, found values as high as 18 per cent. The absolute quantity of dextrose eliminated is also very large.

The absence of the hyperglycemia which accompanies every other form of intense glycosuria was one of the surprising features which impressed the early investigators. Von Mering himself established the fact, and it was confirmed by Minkowski, Levene, Czyhlarz and Schlesinger, and others. On the other hand, Pavy (1*A*) found a slight hyperglycemia. Biedl and Kolisch claimed to demonstrate hyperglycemia and an increased production of sugar in the liver. Milne and Peters (2) have found hyperglycemia, even to a degree which in their opinion accounts for the glycosuria. While hyperglycemia may sometimes exist, the general opinion regards it as occasional or accidental; it is not the essential cause of phloridzin glycosuria. On the other hand, the claims of very low blood-sugar in phloridzinized animals have not been verified. It is a fact well supported by the investigations of Junkersdorff (1) in dogs and of Erlandsen (1) in rabbits, that under normal conditions phloridzin produces practically no change in the blood-sugar. Gabritschewsky found that in phloridzin glycosuria the leukocytes failed to enrich themselves with glycogen, as they do in glycosurias associated with hyperglycemia.

Phloridzin glycosuria is not dependent upon glycogen of the liver nor of any other part of the body, nor upon the integrity of any nervous mechanism or of any organ except the kidneys. Kumagawa and Miura state that slightly smaller doses of phloridzin suffice for glycosuria in fasting than in fed animals. Von

Mering produced phloridzin glycosuria in dogs starved for 10 or 12 days, and later observers have obtained glycosuria after ninety days' starvation. The quantities of sugar excreted have been proved under suitable conditions [Cremer, Moritz and Prausnitz, Kraus, Lusk] to be a multiple of any quantity of glycogen possibly present in the body. Minkowski [(1), p. 53] found that the glycosuria of depancreatized dogs at the height of diabetes was markedly increased by phloridzin, and was also elevated if it had already begun to decline as a result of weakness. Hedon (4) confirmed this observation, and carried it farther by showing that totally depancreatized dogs, almost at the point of death and free from glycosuria because of advanced weakness, are made glycosuric by phloridzin. It is therefore certain that the pancreas is not the point of attack of phloridzin. Phosphorus is a poison known to damage the liver, and, according to some later writers, also the adrenals. Yet v. Mering poisoned dogs with phosphorus to the point of extreme fatty degeneration of the liver, and found that phloridzin administered 9 hours before death caused abundant glycosuria. Ray, McDermott and Lusk proved that phosphorus poisoning has little or no effect upon the sugar-elimination from phloridzin. Frank and Isaac (4) by means of phloridzin glycosuria in phosphorus-poisoned dogs, were able to reduce the animals to almost complete aglycemia. Opium diminishes phloridzin glycosuria (Gigon). Eppinger, Falta and Rudinger (1) found that phloridzin causes little or no glycosuria after removal of both adrenals; but Gautrelet and Thomas (1) and also McGuigan (2) found that glycosuria occurs very readily under these conditions. The latter findings are in harmony with all the other known facts concerning phloridzin. Aschner has found phloridzin glycosuria unaffected by hypophysectomy. Phloridzin glycosuria is unaffected by cutting the splanchnic nerves. It also occurs, as proved by Lepine [(1), p. 279] after section of the spinal cord in the lower cervical region. After corrosion of the liver by injection of dilute sulphuric acid into the ducts, Pick found phloridzin glycosuria still obtainable. Rosenfeld (5) alleges that phloridzin glycosuria is absent in Eck-fistula dogs; he also claims that frogs show no phloridzin glycosuria after extirpation of the liver, though his normal frogs showed it. It is unavoidable that these, like some other recent claims of Rosenfeld, must be rejected. Even if the liver were indispensable for phloridzin glycosuria, it is well known that the Eck fistula does not completely exclude the

liver from metabolism. The results in frogs must be understood as accidental occurrences in a series comprising too few experiments [*e.g.*, Külz and Wright failed to obtain phloridzin glycosuria even in normal frogs], or else as the consequences of renal or other damage during the operation; for the testimony on the other side is both abundant and convincing. Von Mering excluded the liver by ligation of vessels, or actually excised it in geese which had fasted 2 or 3 days, and under these conditions obtained glycosuria as high as 1 per cent. The results of Thiel were similar. Langendorff seems to have been the first to observe phloridzin glycosuria after extirpation of the liver in frogs. He labored under the impression that he was confirming previous work of von Mering, but von Mering never used frogs for this purpose. Leschke (5) has recently repeated this work, with positive results. De Domenicis (2) ligated the vessels to various organs, including the liver and the brain, and found no effect upon phloridzin glycosuria. The most thorough and radical undertaking in this connection was that of Pavy, Brodie and Siau. In dogs, they removed entirely the liver, pancreas, spleen, stomach, and intestines, and ligated the subclavian and vertebral arteries and the aorta below the renal arteries. On injection of phloridzin, such a fraction of a dog reacted with glycosuria of over 4 per cent.

Grube (7) claimed that perfusion of livers with phloridzin not only prevents formation of glycogen from dextrose, but also breaks down part of the glycogen already present. Schöndorff and Suckrow, repeating these experiments, failed to confirm the findings; they assert that phloridzin has no influence upon glycogen-formation. Grube (8) found that in phloridzin glycosuria, the glycemia being normal or slightly above normal, the liver-glycogen was diminished, and this diminution was greater than the amount of sugar excreted. When both kidneys were ligated off or extirpated, the blood-sugar was found normal or slightly below normal, and the liver-glycogen was diminished. Grube believes in a specific effect of phloridzin upon the liver, and considers his position supported by the well-known fatty changes. But since phloridzin glycosuria occurs in absence of the liver, any such possible effect need not be considered of primary importance.

Loewi (4) epitomizes the behavior of liver-glycogen. At the height of maximal phloridzin glycosuria, the liver contains no glycogen (or bare traces). When the effect is not maximal, or when the animal is killed during decline of the glycosuria, or when

the utilization of glycogen has been prevented by some narcotic, a certain amount may be found in the liver. But when glycosuria is prevented by removal of the kidneys, a considerable amount of glycogen may be found in the liver.

The essential action of phloridzin is exerted upon the kidney. Minkowski [(1), pp. 63–68] demonstrated the different effects of ligating off the kidneys in depancreatized and in phloridzinized animals. In the former, the blood-sugar rose, even above 0.6 per cent; in the latter the blood-sugar remained practically normal. Biedl and Kolisch claimed to find, along with general hyperglycemia, an increase of sugar in the blood of the hepatic veins, indicating an increased sugar-formation in the liver. Some authors, *e.g.*, Gigon, still argue for a direct hepatic action of phloridzin. Underhill (6) has lately corrected some of the earlier work, by using maximally phloridzinized animals. He finds that hyperglycemia is produced when the kidneys are thrown out of function, either by complete ligation in dogs or by means of sodium tartrate nephritis in rabbits. This hyperglycemia is not as great as in depancreatized animals, but yet indicates a specific stimulation of sugar-production by phloridzin. The importance of the specific renal action is recognized by Underhill. Since the sugar-excretion from phloridzin is a multiple of that which could result from simple hyperglycemia, and since the glycosuria occurs in glycogen-free animals and under conditions which ordinarily paralyze the sugar-regulating mechanism, the action upon the kidney must be regarded as the essential one.

Loewi (1), also Kohler, found that changes in temperature are without effect upon phloridzin glycosuria. Lusk (1) found that neither cold nor mechanical exercise exerts any influence.

Although in one way entirely independent of the bodily reserves and of the diet, phloridzin glycosuria in another way bears special relations to both of these. Though pronounced glycosuria occurs in animals after any length of starvation, yet the excretion is much less than in well-fed animals. In any animal possessing glycogen, the first effect of phloridzin is the greatest. After this first rush of glycosuria, which is supposed to indicate a "flushing out" of carbohydrate reserves, the glycosuria diminishes, unless it is kept up by frequently repeated doses. By subcutaneous doses repeated regularly every eight hours, it is possible to keep dogs at the height of phloridzin glycosuria for prolonged periods, as demonstrated and used in valuable manner by Lusk.

In this connection, brief mention must be made of the remarkable *quantitative relations* of the effects of phloridzin. An animal on a definite diet receives a definite dosage of phloridzin; it reacts with a definite sugar excretion, which can be maintained as long as desired under the given conditions. But this is not the maximum glycosuria obtainable on this diet. By increasing the dose of phloridzin, the sugar-excretion is increased, but not in proportion. Each successive increase of dose produces a smaller increment of sugar-excretion, till finally a maximum is reached, beyond which an increase of dose is unavailing. Likewise, with the original dose of phloridzin, the glycosuria is not the maximum which that dose can produce. Increase the diet by either carbohydrate or protein, and the sugar excretion is increased, though the dose of phloridzin remains the same. But with each successive increase of the diet, the increment of sugar-excretion is less, till finally a limit is reached which is the maximum for the given dose of phloridzin. Increased glycosuria is then obtainable only by increasing the phloridzin. These laws therefore, as determined by Loewi (1 and 4) and by Stiles and Lusk, are briefly expressed as follows. First, as regards phloridzin, a given dose poisons only for a given quantity of sugar-forming material, not maximally. Second, as regards sugar and foods which yield it, phloridzin produces no intrinsic impairment of utilization. Phloridzin compels the excretion of more or less dextrose through the kidneys; but when this demand is fully satisfied, the phloridzinized animal is able to utilize sugar just as readily as any other animal. Here of course is a fundamental difference from diabetes. It is brought out very clearly in the recent work of Ringer (4). Giving of sugar in a phloridzinized dog spares protein, even though the sugar be quantitatively excreted. In a depancreatized animal sugar has no sparing power.

Dextrose fed to a maximally phloridzinized animal within the limits above mentioned is quantitatively excreted. Levulose, galactose, lactose, etc., are not excreted as such, but in the form of dextrose. [See Reilly, Nolan and Lusk.] Sugar-formation from cellulose has been demonstrated by feeding cauliflower to dogs and paper to goats. The ability to utilize pentoses is said to be much increased in phloridzin glycosuria.

It may be noted that birds, in which hyperglycemia causes little or no glycosuria, react to phloridzin with well-marked sugar-excretion. According to Kossa (2), chickens treated with

phloridzin eliminate dextrose not only in the urine but also in the feces.

Cremer found that phloridzin does not increase the lactose-secretion of the mammary glands. Cornevin has made the opposite assertion. The former statement is more commonly accepted.

The most recent study of the relation of phloridzin glycosuria to food is that of Roth. Using minimal doses of phloridzin intramuscularly in dogs (0.001 g.), he found that the glycosuria begins latest and the sugar-excretion is least in fasting or fat-fed animals. Protein, fed as pure casein, increases the glycosuria. The increase of glycosuria was no greater after 500 g. meat than after 250 g. meat (because of the small dose of phloridzin). Feeding of 100 g. bread increased it more than the above meat-feeding. The greatest excretion was after 50 g. dextrose; here in some cases the excretion was thrice that from meat. The glycosuria is greatest during the first 3 hours after feeding; 12–15 hours after feeding, *i.e.*, in the period of greatest glycogen richness, the glycosuria is at its minimum.

B. Fat Metabolism.

The principal question in this connection is whether sugar can be formed from fat in the animal body. Phloridzin poisoning is a favorite method for attacking this problem, which is still not fully decided. The most numerous and best-established researches seem to be negative. Two fundamental facts are probably the chief source of encouragement for the minority who support the affirmative; first, that fat is formed from carbohydrate in the animal body, therefore the process may possibly be reversed; second, that plants form carbohydrate from fat, therefore possibly the animal body may do likewise.

Von Mering decided against fat as a source of sugar, because glycosuria falls as low on fat-feeding as on starvation. Moritz and Prausnitz, also Cremer and Ritter, came to the same conclusion. Kumagawa and Miura supported this view by experiments with dogs on prolonged starvation. Roth has found that fat-feeding does not increase phloridzin glycosuria.

Contejean took the opposing position, but his argument was merely that the D : N ratio in phloridzin glycosuria may be higher than 2.8, which is now conceded by all without affecting the

question. Hartogh and Schumm, however, came to results which would have been decisive if correct, for their values of D/N ranged from 5 to 13, and would have ruled out albumin as the sole source of the sugar. Cremer proved that glycerin is a source of sugar, but not fatty acids. Schmidt attempted to decide if sugar may yield glycerin; he therefore fed fatty acids to phloridzinized dogs, on the chance that glycerin formed at the expense of sugar to combine with these acids might reduce the glycosuria. He found diminution of sugar-excretion, but a corresponding fall in the nitrogen, and therefore concluded that the fatty acids did not affect the carbohydrate economy directly, but served merely to spare protein.

Lusk is the one in particular who overthrew the results of Hartogh and Schumm, and who has supported most strongly the view that fat does not yield carbohydrate in the body, at least in phloridzin poisoning. [See Lusk, Arteaga and Lusk, Mandel and Lusk, etc.] It is shown in particular that fat-feeding of phloridzinized animals does not alter the D/N ratio, which is constantly 3.65/1; the calories lost in the urinary sugar are compensated by increased protein metabolism; and in respiration experiments, a phloridzinized dog whether fasting, or fed on meat alone, or on fat alone, or on meat and fat together, burns no more fat than the same dog when fasting without phloridzin. The comprehensive and conclusive nature of these researches would seem to close the case, at least for phloridzin.

Lommel devised a method in which he attempted to exclude oxidation of body-fat by substitution of alcohol. He himself does not claim to have proved definitely that fat yields sugar. The strongest affirmative work of recent years is that of Junkersdorff (2). He takes up the question along Pflüger's well-known lines, and presents a series of experiments with phloridzinized dogs on starvation and on fat-feeding. The values found for D/N are frequently far above 7. The results are taken to mean production of sugar from non-protein material, *i.e.*, fat. Derivation of sugar from protein, and relations of definite character between D and N, are acknowledged by Junkersdorff, but the claim is made that part of the sugar excreted must come from fat.

As is well known, von Noorden still maintains the formation of sugar from fat. Grafe and Wolf are the latest to present figures supposedly proving sugar-formation from fat in severe human diabetes.

Other features which may be mentioned concerning the fat economy in phloridzin poisoning are lipemia and acidosis. Lattes (2) found that fasting dogs show a slight increase of fat in the blood, and that in fasting phloridzinized dogs there may be a lipemia amounting to three times the normal blood-fat. This fat comes from the depots, and represents an abnormal mobilization.

Concerning acidosis, the earlier investigators came to discrepant results. Baer cleared up the matter, by showing that phloridzinized dogs are free from acidosis as long as they are in nitrogenous equilibrium. When food is insufficient, acidosis appears. Either carbohydrate or protein added to the diet will remove it. All three of the acetone bodies have been found by different observers in the urine of under-nourished phloridzinized dogs.

C. Protein Metabolism.

Von Mering discovered that meat-fed phloridzin-animals excrete fully as much sugar as those on carbohydrate diet. Moritz and Prausnitz found the same. These results, obtained by the less exact method of feeding phloridzin, are somewhat modified by the above-mentioned work of Roth with intramuscular injections. The peculiar *quantitative relations*, previously mentioned, hold for both carbohydrate and protein food.

Phloridzin produces no direct effect upon protein metabolism. Any such thing as a "toxic" decomposition of protein by it was ruled out by Moritz and Prausnitz, and Loewi (4) presents tables to the same effect. The increase of nitrogen excretion caused by phloridzin under certain conditions is due to (1) fever resulting from subcutaneous injection, and not present if the drug is given by mouth; (2) secondary breaking down of protein to replace the urinary loss of sugar, in fasting or insufficiently fed animals. This secondary increase of fasting nitrogen may amount to 3 or 4 times the normal. When animals are free from fever and receive sufficient protein or carbohydrate food, they show no increase of nitrogen excretion from phloridzin. Sugar spares protein in the phloridzinized as in the normal animal.

In phloridzin poisoning, apparently a larger portion of the protein molecule is transformed into sugar than in "total" diabetes. The D/N ratio established by Minkowski in depancreatized dogs was about 2.8 or 3. In fasting, "maximally" phloridzinized dogs,

Lusk has proved that the D/N ratio is 3.65 or 3.75, *i.e.*, about 60 per cent of the protein is excreted as sugar, as opposed to 45 per cent in diabetes. There are differences between animal species [see Arteaga and Lusk, together and separately]. As opposed to the above figure for dogs, the D/N value in phloridzinized cats, goats, and rabbits is 2.8, *i.e.*, the same as the *diabetic* ratio in dogs.

The relations of different protein substances and their derivatives as sources of sugar have also been studied by means of phloridzin. In this connection the work of Bendix, Knopf, Kraus, Lusk and Stiles, and Glaessner and Pick (1) may be referred to. As sources of sugar have been established casein, egg-white, fibrin, serum, gelatin, peptone, the mixed end-products of pancreatic digestion, and individual amino-acids (leucin, asparagin, alanin, glycocoll, and glutamic acid). Glaessner and Pick found some of these to yield sugar in fed but not in fasting animals. Acetamid, uric acid, and urea have been found negative as sources of sugar. The conclusions of Ringer and Lusk may be quoted, as follows. Glycocoll and alanin can be changed completely into dextrose. Three carbon atoms of aspartic acid and of glutamic acid can be changed into dextrose. Tyrosin yields no dextrose, but increases the β-oxybutyric acid in the urine. Glucosamin yields no dextrose. Glyceric acid and propyl alcohol yield dextrose, but acetic acid yields none.

D. General Metabolism and Diuresis.

Phloridzin is practically free from harmful effects in the body. Mention was previously made of writers who have given the drug to animals for months in succession; and von Mering gave it to a human patient for 30 days without damage. Schwarz found phloridzin highly toxic for rats after epinephrectomy.

The respiratory exchange was found by Ouchinsky unaltered. Lusk, and Mandel and Lusk, found in respiration experiments that there is in general no action of phloridzin on metabolism except that due to the loss of sugar; this loss is compensated in the fasting animal by increased protein katabolism. Oxidation of fat is diminished.

La Franca, comparing the respiratory exchange in different forms of glycosuria, found that in the case of phloridzin the absorbed O_2 and the excreted CO_2 are both diminished. Phloridzin

is thus distinguished from adrenalin and diabetic (after pancreatectomy) glycosuria, in which both these values are increased. The respiratory quotient was found to be diminished in phloridzin glycosuria and in experimental diabetes, and unchanged in adrenalin glycosuria. Belák has lately reported that phloridzin in doses not "toxic" increases greatly the renal labor, but also causes increased O_2 consumption in other organs. It therefore increases the energy-exchange. It may also have a "toxic" action; then the O_2 consumption and the blood-pressure sink.

Levene described changes in the albuminous constituents of the blood in phloridzin poisoning, the serum albumin being diminished and the globulin increased. Work in this direction with newer methods might be of interest.

Wolf and Osterberg have recently made studies in "maximally" phloridzinized animals concerning the excretion of kreatin, kreatinin, ammonia, acetone bodies, and total sulphur. They find in particular that the proportional excretion of kreatin steadily rises.

Glaessner and Pick (2) found that, contrary to the behavior of adrenalin, phloridzin has no influence upon the external secretion of the pancreas. Wohlgemuth and Benzur found no increase of diastase in the blood of phloridzinized rabbits, but claim a marked increase of diastase in the kidney. This line of research is probably fruitless, as noted in Chapter II.

The earliest workers found phloridzin to be a diuretic, and it is commonly accepted as such; but dispute still exists on the subject. Loewi (2) holds that it is not a direct diuretic, but that diuresis results from the osmotic action of the sugar in the renal canaliculi, preventing the resorption of water. Accordingly, the excretion of chlorides is not increased. In the papers of Biberfeld (1) and Frey may be found a discussion covering this point. Against the finding of Biberfeld, that phloridzin inhibits chloride excretion, Loewi and Neubauer maintain that phloridzin, contrary to other diuretics, does not influence NaCl excretion, and in particular does not inhibit it.

Huot found phloridzin to be a powerful diuretic, the urine after a subcutaneous dose of 5 mg. rising to four times the normal [size of dog not stated]. This polyuria was accompanied by a great increase of excretion of urea, chlorides, and phosphates. The elimination of subcutaneously injected methylene blue and sodium salicylate was accelerated by phloridzin. Concerning potassium

iodide he was unable to decide, because its excretion was so rapid in both phloridzinized and normal dogs.

Lepine [(1), pp. 272 ff] maintains that phloridzin is not a diuretic at all. It failed in his experiments to increase the excretion of rosaniline trisulphate injected subcutaneously. Also, dogs on a fixed chloride régime were given doses of phloridzin insufficient for glycosuria, and the chloride elimination remained unaltered. When doses large enough for glycosuria were given, the excretion of chlorides and of other urinary constituents was increased, owing, in Lepine's opinion, to the diuretic action of the sugar. Only the phosphoric acid elimination is diminished, which always varies inversely with the chlorides. Biberfeld's results are explained as due to irritation, and Schilling is quoted as having found no relation between the glycosuria and the polyuria in phloridzin-animals.

Spiro and Vogt found that intravenous injection of phloridzin along with dextrose results in a prompt diminution of urine, not due to alteration of blood-pressure. The freezing point of the urine is little changed, because though the sugar percentage rises, the excretion of salts (chlorides, phosphates) is diminished. A similar result follows when phloridzin and sodium chloride are injected together. But if phloridzin is injected alone, the result is pure diuresis, which may be kept up for hours, the freezing point of the urine not rising, in spite of its sugar content. Similar results have been found by Spiro with other diuretics. The conclusion therefore is that phloridzin is a diuretic, but yet can suppress an existing diuresis.

It may be worth noting that the findings of Spiro and Vogt may be interpreted against the view that phloridzin produces diuresis through the agency of sugar. Some diuretics may, as stated, suppress an existing diuresis, but so far as I am aware, dextrose (intravenously) has no such action.

Brodie and Cullis found phloridzin to be a diuretic. The latter also performed perfusion experiments; she found that phloridzin alone produces far more active diuresis than dextrose alone, but addition of a little dextrose to the phloridzin solution increases the diuresis markedly.

E. Fate of Phloridzin Itself.

Very small doses of phloridzin suffice for glycosuria. In dogs, doses of a few milligrams are positive; and Roth in a long

series of dogs, some of them rather large, has found 1 milligram invariably productive of glycosuria. Man is considered even more susceptible than the dog; doses of 0.01 g. are frequently used for diagnostic tests. Rabbits are somewhat less susceptible, and doses of 0.1 to 1 gram are required. Increase of dosage increases the glycosuria within the limits heretofore described, and very large doses can be tolerated. Von Mering gave as much as 10 g. in dogs. Lepine [(1), p. 262] records an experiment with intravenous injection of 10 g. phloridzin in a "small" dog, weight not given; there were no symptoms except temporary weakness and salivation. Leschke (2) found that rabbits commonly die from intravenous injection of 1 g. phloridzin, and Lusk (1*A*) observed several deaths of these animals from 0.25 g. phloretin intravenously. Loewi (4) states that spasms, vomiting, and other symptoms sometimes described as results of subcutaneous injections of phloridzin in dogs can be avoided, even in experiments lasting for months, by care in giving the injections.

It is naturally of interest to know how the body disposes of these doses, large or small. Von Mering early established the fact that glycosuria is not due to the glucose split off from phloridzin, because a dose of the glucoside may cause the excretion of many times the quantity of sugar which it represents, and also because phloretin can produce glycosuria. Minkowski suggested that the kidney may split phloridzin into phloretin and dextrose, and the dextrose may then be excreted while the phloretin combines with fresh sugar, and thus the process may continue. This idea has become sufficiently improbable that it need not be considered among the theories of the mechanism of phloridzin. Charlier did indeed find that the horse's kidney can split phloridzin, but this is a peculiarity of the equine species; the kidney of the dog, an animal more susceptible to phloridzin, is unable to split it. Furthermore, phloridzin injected parenterally is excreted unchanged. After earlier workers [see Glaessner (1)] had debated this point, Yokata brought definite proof of the practically quantitative elimination of subcutaneously injected phloridzin in the urine. Phloridzin taken by mouth is decomposed in the intestine in such manner that much of it fails to be recovered in the urine.

It appears probable that the excretion of phloridzin and of sugar are coterminous. Moritz and Prausnitz believed that phloridzin is excreted after glycosuria has ceased, and Wierdsma claimed that sugar excretion continues after phloridzin excretion

has ceased. Cremer and Ritter found that excretion of sugar and of phloridzin end simultaneously. Erlandsen (1) determined that the maximum phloridzin excretion coincides with the maximum sugar excretion, and was unable to decide exactly whether one disappeared from the urine before the other.

Since the phloridzin is thus excreted unchanged, there is further interest in the question as to what becomes of it in nephrectomized animals. Removal of the kidneys is a method which from the first has been used by a number of investigators for decision of some of the important points concerning phloridzin. It was naturally assumed that the phloridzin under these conditions is present in the body, and exerting all its usual effects except upon the kidneys. Hence, no small importance attaches to the claim of Glaessner and Pick (1) that phloridzin rapidly disappears from the bodies of nephrectomized rabbits.

These authors first gave subcutaneous injections of 2 g. phloridzin in normal rabbits, and bled them to death 2 to 8 hours thereafter, then injected the defibrinated or oxalated blood of each animal into a fresh rabbit, subcutaneously or intraperitoneally. The result in each case was a sugar-excretion of 0.1 to 0.88 g. In another experiment (VII) they injected a rabbit with 2 g. phloridzin subcutaneously at 10:30 a.m., and sacrificed it at 12:30 p.m. An alcoholic extract was made of the defibrinated blood, liver, and kidneys separately, each extract evaporated to dryness and the residue dissolved in water with soda, and each solution injected into a dog. The dogs showed glycosuria as follows:

Blood-extract	1.1 per cent	= 3.3 g. dextrose.
Liver-extract	0.3 per cent	= 2 g. dextrose.
Kidney-extract	0.66 per cent	= 1.5 g. dextrose.

From these experiments it is concluded that in the case of normal animals, injected phloridzin circulates in the blood and is contained in the organs in demonstrable quantity. The authors then apply the same methods to nephrectomized rabbits. In these animals, with doses not above 2 g., the defibrinated blood and the various extracts failed to cause any trace of glycosuria in either dogs or rabbits. For example, in Experiment I of their nephrectomized series (p. 485 ff), they inject a rabbit with 2 g. phloridzin at 11:20 a.m.; they kill it at 4:30 p.m., and the animal-tests for phloridzin in blood and liver are negative. In Experiment II they inject a (nephrectomized) rabbit with 1 g. phloridzin subcutaneously at 3:30 p.m.; they sacrifice it the next day at noon, and the defibrinated blood causes no glycosuria in a fresh rabbit. In Experiment III, they extirpate both kidneys and inject 2 g. phloridzin subcutaneously at 12 noon; they sacrifice the rabbit at 2:30 p.m., and the oxalated blood injected into a dog causes no glycosuria. In Experiment IV, they inject 3 g. phloridzin subcutaneously in a nephrectomized rabbit at 1 p.m., kill it at 6 p.m., and the blood produces glycosuria of 1 per cent (6 g.) in a dog, but the liver yields a negative result. In Experiment V, they inject 2 g. phloridzin subcutaneously in a nephrectomized rabbit at 10:30 a.m., and kill it after 24 hours; the extracts of blood

and liver fail to produce glycosuria in dogs, and furthermore the vanillin-HCl reaction for phloridzin is negative in each extract. In Experiment VI, everything is as in Experiment V, except that the dose here is 3 g. phloridzin. In this case, killing the animal after 24 hours, they find that the liver-extract gives a positive phloridzin-color with vanillin-HCl, and, when injected into a dog, produces glycosuria of 8 per cent the first day and 1.5 per cent on the second day. Thinking that the phloridzin may have entered into some occult combination in the body, they tried under suitable conditions to split such possible compounds by boiling the organ-extracts with various acids, but with negative results. They conclude that the presence of the kidneys is necessary to the preservation of phloridzin in the body. In normal animals, phloridzin circulates and reaches the kidneys unchanged; but in nephrectomized animals it completely disappears in doses below 3 g.

These results appeared improbable to Pflüger, and he delegated Leschke to test them.

Leschke (2) assumed deficient absorption of the subcutaneously injected phloridzin in nephrectomized animals as the cause of the negative results in such animals. As evidence for the slowness of absorption after nephrectomy, he referred to findings of Glaessner and Pick, viz., Experiment IV, in which the blood taken after *five* hours produced glycosuria of 1 per cent, and Experiment VI, in which the blood taken after *twenty-four* hours produced glycosuria of 8 per cent. To avoid difficulties of absorption, Leschke injected rabbits with 1 g. phloridzin or more, intravenously; but the poison resulted in immediate death of all the animals except two. One of these was bled to death 9 hours after nephrectomy and injection, and the blood injected into a dog produced glycosuria of 0.1 per cent. The other rabbit underwent nephrectomy and intravenous injection of 1.2 g. phloridzin, and was bled to death after $9\frac{1}{2}$ hours. The blood injected into a dog produced glycosuria of 0.2 per cent. Leschke also performed two experiments with subcutaneous injection. In the first, a nephrectomized rabbit received 2 g. phloridzin subcutaneously, and was killed after 4 hours. The œdematous connective tissue at the site of injection gave a positive vanillin-HCl test for phloridzin, and traces were found in the blood and liver. In the second experiment, a nephrectomized rabbit received a subcutaneous injection of 1 g. phloridzin, and was bled to death $8\frac{1}{2}$ hours later. By chemical test, the liver was negative for phloridzin, and the blood contained a trace. The œdematous connective tissue at the site of injection was extracted, and the extract injected into a dog produced a "green reaction" in the urine. Leschke concludes that the findings of Glaessner and Pick are due to deficient absorption of the subcutaneous injection after nephrectomy.

A polemic then ensued between Glaessner and Pick (3) and Leschke (3), without further experiments. In the meantime also appeared a note by Schöndorff (2), disclaiming responsibility on the part of Pflüger or his Institute for Leschke's publication.

In this connection should be mentioned a report by Esau, to the effect that in human patients injected with phloridzin in parts rendered hyperemic by Bier stasis, there is partial destruction of the phloridzin, as indicated by diminished glycosuria.

The effect is not due to dilution with œdema-fluid, for phloridzin injected in a large quantity of salt solution causes greater, not less, glycosuria.

Attention should also be paid to a research by Lepine and Boulud (3) [described also by Lepine (1), p. 291 ff]. These authors found that intravenous injection of alcoholic extracts of various organs, evaporated to dryness and redissolved in water, caused glycosuria in dogs amounting to an excretion of 3 g. dextrose or more. Mention may also be made of my experiments with subcutaneous injection of various organ-extracts, described in Chapter XVIII. Subcutaneous injection of these aqueous extracts was found to result in glycosuria.

For critical purposes, Leschke's findings may first be considered. In his subcutaneously injected animals, his tests of the connective tissue at the site of injection, after 4 and $8\frac{1}{2}$ hours respectively, showed only traces of phloridzin remaining out of doses of 2 g. and 1 g. respectively. The claim of Glaessner and Pick (3) is therefore justified, that Leschke himself has demonstrated the rapid absorption of phloridzin in nephrectomized animals. His claim regarding the presence of phloridzin in the blood rests essentially upon one chemical test (p. 336), which may well be considered doubtful, especially as the liver-extract in this case was negative. The glycosuria in all of his three dogs is so very faint that it may easily be attributed to the mere toxicity of the organ-extracts, independent of phloridzin, unless such an assumption were ruled out by control experiments, which were not done. It might further be urged that after the intravenous injections, the rabbits were too weak to dispose of the phloridzin in "normal" manner. Leschke's evidence is therefore defective.

Glaessner and Pick mention a large number of control experiments for their work, so that although the glycosuria reported is frequently only a trace, it may perhaps be looked upon as a phloridzin glycosuria rather than a toxic glycosuria. But the experimental procedure is somewhat complex, and unknown disturbing elements might conceivably enter in. For example, the importance of sound kidneys for uniform results with phloridzin is well known. Suppose that "nephrotoxic" substances accumulate in the bodies of nephrectomized rabbits; it is conceivable that the extracts of their organs, injected into other animals, might suffice to prevent the faint glycosuria in question. When the amount of phloridzin is higher (*i.e.*, when the animals

had received 3-gram injections) this slight change in the kidney is overcome, and the characteristic glycosuria occurs. Glaessner and Pick present only one experiment (Experiment V) in which the vanillin-HCl test turned out negatively. This experiment fails to demonstrate any peculiarity on the part of nephrectomized animals. It is known that many poisons are destroyed in the body (*e.g.*, by the liver, perhaps also by the body-fluids, according to Esau). Ordinarily, phloridzin does not circulate long, but is excreted rather quickly after absorption. The test in this Experiment V was not performed till after 24 hours. If there were any way to make a dose of 2 g. phloridzin remain for 24 hours in the body of a rabbit with sound kidneys, we might find a destruction of the poison here also. This single experiment with the vanillin reaction therefore does not demonstrate any peculiarity of nephrectomized as compared with normal animals.

The position of Glaessner and Pick is improbable, as Pflüger perceived. First, the general idea is improbable, that nephrectomized animals develop an absolutely new power of destroying a substance which under other conditions circulates unchanged. Second, the alleged time-relations are improbable. In Experiment III it is alleged that at 12 noon a rabbit's kidneys are removed, and thereafter an injection of 2 g. phloridzin given; and at 2:30 p.m. the animal is killed and the phloridzin has already been destroyed. It is improbable that such a marked physiological change should come on so quickly after this operation. Third, the alleged quantitative relations are especially improbable. In this Experiment III, it is supposed that 2 g. phloridzin is destroyed in less than $2\frac{1}{2}$ hours; and in other experiments the same dose is destroyed within very few hours. But as soon as the dose is raised to 3 g., the animal becomes unable to destroy it. In Experiment V, 3 g. phloridzin is injected, and after 24 hours the liver still contains so much phloridzin that it produces in a dog a glycosuria of 8 per cent. It is highly improbable that an animal which can destroy 2 g. phloridzin in $2\frac{1}{2}$ hours, will contain so much of a 3 g. dose in its liver at the end of 24 hours.

To say that these results are improbable is not equivalent to saying that they are incorrect. If correct, they deserve confirmation, for they indicate some remarkable quantitative relations of phloridzin and a remarkable physiological alteration after nephrectomy. If incorrect, they should be proved so, for some important experiments with phloridzin have been done with neph-

rectomized animals. Underhill's sodium tartrate method would seem to open a valuable opportunity in this direction. At present, it must be recognized that Glaessner and Pick's evidence is not fully adequate to support their intrinsically improbable hypothesis. We are not yet justified in believing that the nephrectomized animal deals with phloridzin in any essentially different manner than the normal animal.

3. Mechanism of Phloridzin Glycosuria.

Because the blood-sugar is not increased, von Mering concluded that phloridzin glycosuria is the result of some abnormal process in the kidney itself. This opinion has been supported by practically all the later investigation. One of the most frequently quoted experiments on the subject is that of Zuntz. His method consisted in injecting a phloridzin solution into the renal artery of one side, and observing that glycosuria began in this kidney promptly, several minutes before it began in the other kidney; and for about half an hour the injected kidney continued to excrete more sugar than the other. The objection of Pflüger [(34) p. 385] that the effect may not have been upon the kidney, but that the injected phloridzin may have been decomposed in the blood into phloretin and glucose, is a portion of a hypothesis which may safely be disregarded. More weight attaches to the other objections mentioned by Erlandsen (1), viz., that secretory disturbances may result from the injection of a quantity of fluid into a renal artery, and also that increased diuresis in one kidney inevitably results in a quicker appearance of sugar in the flow from that ureter. But it is still a reasonable conclusion from Zuntz's work that the one kidney shows an earlier and more intense effect because it is poisoned earlier and more intensely than the other, and perhaps even a certain amount of phloridzin continues for some time to cling to this kidney.

The quick appearance of glycosuria after injection of phloridzin into the renal artery is in accord with the quickness after subcutaneous injection. Ray, McDermott and Lusk found that saccharine urine is obtainable from a dog's bladder $5\frac{1}{2}$ or 6 minutes after a subcutaneous phloridzin injection. Such rapidity distinguishes phloridzin glycosuria from all forms which depend on a primary effect upon the glycogen-storing organs.

Schabad observed that phloridzin glycosuria diminishes but does not disappear in the nephritis produced by potassium bi-

chromate. Rosenberger (p. 84) quotes authors who have found that phloridzin glycosuria is diminished by aloin or piperazin, but not by arsenic, chromic acid, or hirudin. Renal lesions in experimental animals are known to have strong influence in diminishing the glycosuria, and the importance of using fresh animals with sound kidneys has been emphasized by Lusk. Greater than any of these influences is the effect of glutaric acid, as discovered by Baer and Blum (1). This substance is able to bring phloridzin glycosuria almost or quite to disappearance. Tartaric and other dicarboxyl-acids were found by Baer and Blum (3) to have a similar effect. These authors in their first paper considered the effect due to a specific action upon the formation of sugar in the body, and they adhered to this view in their paper (2) in argument with Wilenko. Wilenko (1 and 2) maintained that the action of glutaric and related acids is upon the kidney, and this view has become established. It is supported by the finding of Starkenstein (3), that tartaric acid tends to diminish the glycosuria of adrenalin and of dextrose injection. Ringer (3) was unable to confirm the findings of Baer and Blum; in his experiments glutaric acid had no effect in reducing the excretion of sugar, nitrogen, or acetone in phloridzin glycosuria. Underhill (5) explained the negative results of Ringer as due to the giving of glutaric acid in divided doses, so that the kidneys were not sufficiently injured. Using sodium tartrate, Underhill confirmed the observations of Baer and Blum, and demonstrated that the effect is due to nephritis. The suppression of urine was sufficient to account for the diminished excretion of the various urinary constituents. In some extreme instances there was anuria; in others, water-clear 24-hour specimens of urine of fair volume were obtained, containing no trace of either dextrose or nitrogen. Microscopically, the tubular cells of the rabbits' kidneys showed necrosis; those of the dogs showed vacuolization. The changes were no greater in animals receiving tartrate plus phloridzin than in animals receiving tartrate alone. The nephritis is therefore a specific effect of the sodium tartrate.

Kossa (3) found that asphyxia or severe dyspnea produced by CO_2 inhalations, artificial pneumothorax, and other means does not diminish the amount of urine of a phloridzinized rabbit, but does diminish the sugar-excretion to about half. Carbonated (CO_2) water injected subcutaneously has a similar effect. Cutting the renal nerves on both sides causes the sugar excretion to fall

to a minimum or even disappear. Kossa refers the effects of dyspnea and CO_2 to action on the renal nerves, which in his opinion not only control the blood-vessels but also govern the functions of the renal epithelium. Most physiologists do not recognize true secretory nerves to the kidneys; but Kossa's experiments may at least be added to the series showing the intimate relationship between phloridzin glycosuria and renal activity.

The direct action of phloridzin upon the kidney is the basis of its sole clinical usefulness. Schaller [ref. by Glaessner (1)] employed it to decide whether the unborn child urinates. By injecting phloridzin into the mother before birth, and at delivery testing the amniotic fluid for sugar, he arrived at the conclusion that there is no intrauterine passage of urine. But it is in diagnosis, viz., as a test of renal efficiency, that phloridzin has chiefly been called into service. Klemperer introduced it, and Casper and Richter elaborated the method by using it in conjunction with ureteral catheterization. The value of the procedure is still somewhat disputed, in respect to diagnosis of bilateral renal disease, and also of disease limited to one kidney. Essentially two factors have been considered in the performance of the test, one the degree of glycosuria produced by a given dose in either or both kidneys, and the other the length of time before glycosuria appears. There is delay in the onset of glycosuria in nephritic patients, and also to some extent in aged persons. In the paper of Salomon will be found a list of other conditions besides nephritis (lowered blood-pressure, disturbances of renal innervation, carcinoma, arteriosclerosis, liver disease, etc.) which delay phloridzin glycosuria and thus confuse the diagnosis. For discussion of the general usefulness of the phloridzin method, reference may be made to the papers of Rowsing and of Israel for the negative, and of Casper and Richter, F. Strauss, Barth and Kapsamer for the affirmative side. The most common clinical view probably is that the phloridzin test is not entirely worthless yet never absolutely reliable; it is a supplementary test. From the experimental side, Roth has questioned the validity of the test, on the basis of variations shown by different normal dogs and by the same dog at different times. With the same minimal dose of phloridzin, the same animal may on one occasion excrete several times as much sugar as on another occasion. The time of onset and the duration of excretion were variable in the same animal on differ-

ent diets. It was found that the differences between different individuals are so great that accurate comparisons are impossible.

Granting that the kidney is the seat of action of phloridzin, the important question then is how the process takes place. Some earlier ideas have been discarded, such as the hypothesis of Minkowski concerning a splitting into phloretin and glucose, and the suggestion of Kolisch and Stejskal, and of Pflüger, that the glucoside may cause decomposition of the jecorin of the blood, thus leading to excretion of the sugar set free. The debate at present is chiefly upon one question. In phloridzin glycosuria, is the sugar of the urine derived from the sugar of the blood, or from some other substance? Does the kidney show an abnormal permeability for sugar, or an abnormal tendency to "secrete" sugar, or on the other hand does the kidney manufacture sugar from other substances, or split it off from some loose compound? The former theory appears more probable at first thought, but the second is probably more strongly supported by investigation. It may be noted that whichever view is adopted, there is no valid basis for the comparison frequently made between phloridzin glycosuria and the renal glycosuria sometimes found as a spontaneous clinical phenomenon. The slight leakage of sugar in such patients may be comparable to the glycosuria produced by renal poisons such as uranium; but there is at least no evidence that anything resembling the remarkable phloridzin mechanism is present.

The supporters of the second theory of phloridzin activity have not agreed upon any particular substance from which the excreted sugar is derived. According to Levene, it might be the blood-protein. According to the Pavy school, it is probably some substance present both in the kidney and in the blood. According to Loewi, it is a combined form of blood-sugar; and Lusk accepts this view with the proviso that in this combination the sugar cannot be burned. According to Lepine, the "virtual" blood-sugar is the source from which the kidney splits off dextrose. Full agreement cannot be expected, in view of present hazy ideas. The most important question is that already stated, whether the poisoned kidney develops a tendency to excrete the ordinary blood-sugar, or whether the excreted sugar is derived from some compound, either a large molecule, or some abnormal combination of the blood-sugar. The researches tending to support the respective theories may now be considered separately.

A. Theory of Permeability to Sugar.

The partisans of this theory have devoted their efforts chiefly to proving that hyperglycemia increases phloridzin glycosuria, and that foreign substances are eliminated more quickly with phloridzin than without.

Minkowski discovered, and was confirmed by Hedon (4), that phloridzin greatly increases the glycosuria of the depancreatized dog,* while the hyperglycemia is markedly reduced. But if the kidneys are extirpated, the hyperglycemia is not affected by phloridzin. Lepine [(1), pp. 269–70] further showed that if anuria is produced without removing the kidneys, phloridzin fails to change the hyperglycemia of the diabetic dog. All this might appear to indicate that phloridzin acts by increasing the rate at which the kidneys excrete sugar from the blood. Yet Lepine is not a supporter of this theory.

Gilbert and Carnot (1) worked out a ratio between injected and excreted dextrose. In their paper (2), they found that phloridzin increases the proportion excreted, and that salts of manganese diminish it.

Spiro and Vogt in 1902 reported experiments which they and others have interpreted as supporting the theory of increased permeability. Their findings concerning diuresis have already been mentioned. They gave prolonged intravenous injections of dextrose at a fixed rate, and at a given point made an additional intravenous injection of phloridzin. The latter always caused a marked diminution in the quantity of urine and of its contained salts, while the sugar percentage promptly rose (*e.g.*, from 3.2 per cent it rose to 4.1 per cent; in an extreme case it rose from 3.6 per cent to 7 per cent). They also made the interesting attempt to test the permeability of the kidney for other sugars. By the above method, they found that the excretion of cane-sugar is accelerated by phloridzin; but under these conditions the phloridzin fails to produce glycosuria; its glycosuric action seems to be suppressed by saccharose. But with the same technique, levulose yields the opposite result; phloridzin diminishes the levulose excretion, and causes an excretion of dextrose. It is curious how these experiments could ever have gained universal acceptance as a support for the theory of increased permeability, when they in fact rather support the opposing theory. They fall into three divisions.

First, the dextrose infusion experiments are merely a variation of the study of relations between phloridzin and hyperglycemia. The authors do not even state that an increased *quantity* of dextrose was eliminated; they mention merely an increased percentage in a smaller volume of urine. But granting that two causes of glycosuria produce greater sugar-excretion than one cause, there is still nothing established concerning the phloridzin mechanism.

Second, their results with cane-sugar injections, if correct, are not decisive. Phloridzin is recognized as a diuretic and as facilitating the excretion of certain foreign substances; and if it be true that this diuretic activity applies to cane-sugar, the fact does not necessarily possess any import for the mechanism of phloridzin glycosuria. Incidentally, Spiro and Vogt found phloridzin glycosuria to be suppressed by cane-sugar. Though the finding may be correct for their particular order of experiment, as a general proposition it is incorrect, for parenterally injected saccharose does not ordinarily inhibit phloridzin glycosuria.

Third, the most important feature of Spiro and Vogt's work is that of the levulose injections. Levulose is much more closely related to dextrose than cane-sugar. The fact that phloridzin *diminishes* the excretion of levulose, while causing excretion of dextrose, indicates if anything that the change in the kidney is not a mere increase of permeability to sugar, but an effect of a different nature. At any rate, the levulose finding outweighs the saccharose finding.

Huot next devoted a thesis to establishing the theory of increased permeability. In addition to his previously mentioned results with methylene blue and sodium salicylate, he found that when dextrose is fed or injected subcutaneously, phloridzin glycosuria is increased; and the increase is greater after subcutaneous than after oral introduction, presumably because the glycemia is higher. He showed, moreover, that if a dose of dextrose causes a certain sugar-excretion (a), and if a dose of phloridzin causes a certain sugar-excretion (p), then the same dose of dextrose given simultaneously with the same dose of phloridzin causes a glycosuria which is greater than $a + p$. Phloridzin also diminishes the glycogen-content of the liver. The doses of dextrose used were large [50–80 g. subcutaneously, 350–750 g. intrastomachally in dogs; but it is an error to have omitted the weight of the dogs]. Huot's experiments therefore contribute merely to the two general propositions already stated; one, that phloridzin glycosuria is

increased by hyperglycemia, and the other, that phloridzin as a diuretic may accelerate the excretion of certain foreign substances.

Bang, Ljungdahl and Bohm (3) found that the hyperglycemia following piqûre is diminished but not prevented by phloridzin.

The paper of Erlandsen (1) should be consulted for a review of most of the literature, from the standpoint of a believer in increased permeability. The author proceeds to prove that the hyperglycemia resulting from bleeding is prevented by phloridzin. Erlandsen (2) finds that adrenalin hyperglycemia is not prevented by phloridzin, and supposes that the sugar is formed faster than it can be excreted. Phloridzin increases adrenalin glycosuria, and the glycosuria produced by the two simultaneously is greater than the sum of the sugar-excretion produced by the two separately. He believes not in a passive increase of renal permeability, but in an active secretion of sugar by the kidney from the blood under the influence of phloridzin, and a secondary increase of sugar-production in the liver, for which the diminishing concentration of dextrose in the blood is the effective stimulus. Also in his first paper, to answer a possible objection, he offers mathematical proof that the intensity of phloridzin glycosuria requires the assumption that the kidneys excrete all or practically all of the sugar brought to them in the blood. He says in spaced type (pp. 356–7): "*These experiments accordingly support the assumption that the kidneys at the height of the intoxication excrete all the dextrose carried to them. The renal blood must at this time, practically speaking, give up its entire dextrose content.*" Erlandsen's assumption seems not unreasonable on the basis of his theory, because the glycosuria is so intense. But even though criticism may be directed against the able investigators who have found *more* sugar in the blood of the renal vein than in the arterial blood, their work has at least established the probability that the renal-vein blood is far from being sugar-free. Erlandsen's figures therefore might serve as a weapon to the opponents of his theory.

Starkenstein (3) found that tartaric acid, which diminishes phloridzin glycosuria, likewise diminishes adrenalin glycosuria. But it is possible that the mechanism in the two cases is different. The excretory function of the kidney is evidently damaged by tartaric acid, but other functions may well suffer simultaneously. The possibility that two different renal functions may here be concerned is suggested by the fact that some poisons which produce nephritis and alter the excretory function may fail to affect

phloridzin glycosuria, *e.g.*, chrome-salts. Likewise Wilenko (3 and 5) found that intravenous injection of concentrated salt or sugar solution alters the permeability of the kidney for sugar; and repeated venesections, by reason of hydremia, injure the kidneys so that adrenalin glycosuria is diminished; but none of these agencies alter phloridzin glycosuria.

Roth found that the sugar-excretion in phloridzin glycosuria is increased more by dextrose than by bread or meat feeding. He interpreted his experiments in favor of a simple increase of renal permeability. It seems possible to interpret them otherwise, for two reasons. (1) Reicher performed blood-sugar analyses on Roth's dogs; the fasting values were 0.09–0.12 per cent, but $2\frac{1}{2}$–4 hours after feeding (raw) meat, these figures had risen to 0.14–0.21 per cent. Analyses after dextrose are not given; but it would seem probable that at similar periods after 50 g. dextrose by mouth, in dogs weighing $8\frac{1}{2}$–$11\frac{1}{2}$ kilos, the hyperglycemia would be no greater than this. (2) Roth like others has found the dextrose excretion independent of the water-diuresis. But in forms of glycosuria known to be due to simple excretion of the blood-sugar, increased diuresis regularly produces increased elimination of sugar.

Underhill (6) prevented sugar-excretion in phloridzinized animals, in dogs by ligating the kidneys, in rabbits by sodium tartrate nephritis. In both cases, hyperglycemia resulted. Since this result was the same whether the renal circulation was preserved or not, the author's conclusion is against Pavy's doctrine of the formation of sugar from other materials in the kidney. The experiments do not militate against the view of Loewi and Lusk that the blood-sugar is in some abnormal combination. An adherent of the Pavy school might also argue that the essential process in the kidney is independent and different from the by-effect which gives rise to hyperglycemia.

In summary, the above facts seem insufficient to establish the theory of increased permeability to blood-sugar, for the following reasons.

1. Injected foreign substances are sometimes eliminated more rapidly in consequence of the diuretic activity of phloridzin. But this fact is not decisive concerning the mechanism of phloridzin glycosuria. These substances are not glucose; and the glycosuria and diuresis produced by phloridzin are not parallel.

2. Phloridzin diminishes hyperglycemia, and hyperglycemia

increases phloridzin glycosuria; but these facts again seem inadequate to prove that the glycosuria results from a direct excretion of the blood-sugar by the kidney. A consideration enters in here which has perhaps not been sufficiently regarded. It is obvious that neither the blood alone nor the kidney alone can contain enough sugar-forming material to account for phloridzin glycosuria. If this glycosuria results from the breaking up of some compound, this substance must contain dextrose; and either the substance itself, or its dextrose component, must be renewed from somewhere, and its renewal is presumably easier and more rapid when the supply of sugar is abundant.

B. Theory of Renal Production of Sugar.

Levene in 1894 was the first to claim that in phloridzin poisoning the blood of the renal vein contains more dextrose than the arterial blood. His analyses of the blood also showed "a constant decrease of the general amount of proteids and a varied relation between the serum albumin and the serum globulin. Serum albumin is usually decreased in quantity; serum globulin increased." "Thus the general analysis of the blood seems to show that phloridzin glycosuria does not originate simply in the extraction of sugar from the blood, but that more profound changes in the tissues take place, and that these changes corroborate the views of those authors who see the source of sugar in phloridzin glycosuria in the decomposition of proteids." The experiments of Levene were performed at a date prior to the present more accurate methods of blood analysis, and it is probable that the differences found by him lie within the limits of experimental error.

Biedl and Kolisch reported experiments of perfusion of "surviving" kidneys with blood containing phloridzin. They claimed that frequently the blood-sugar was found to be increased by the perfusion. Details of their work were never published, and this and other results announced by them are now generally considered to be due to experimental errors.

Pavy, Brodie and Siau performed perfusion experiments with dog kidneys. The blood used for perfusion contained phloridzin, and also small quantities of chloral and amyl nitrite as vasodilators to facilitate diuresis. The essential result was that the urine secreted in these experiments contained more sugar than

was lost by the blood. In a further series of experiments, dogs received intravenous injections of phloridzin after ablation of all abdominal viscera; stomach, intestines, liver, spleen, and pancreas were removed, and in some cases the subclavian and vertebral arteries were ligated, and the aorta ligated below the renal arteries. Even under these last, extreme conditions, glycosuria as high as 4.6 per cent was obtained. This percentage of sugar in the urine was obtained when the blood-sugar was only 0.057 per cent. The sugar of the blood was thus diminished; but an entirely similar diminution occurs after ablation of the viscera without phloridzin injections; furthermore the quantity of sugar lost by the blood was only a fraction of the quantity present in the urine. In a third series of experiments, dogs received the usual phloridzin injections after ablation of viscera, till (after about 3 hours), glycosuria had become slight. Intravenous injection of defibrinated blood from a normal dog then caused a marked increase of sugar-excretion, the surplus of excreted sugar being more than the sugar content of the injected blood. Injection of saline had no such effect. The authors compare the action of the kidney, in forming dextrose under an abnormal stimulus, to the action of the mammary gland in forming lactose under a normal stimulus. Pavy [(1), pp. 68–69] supposes that sugar is taken on by protein as a side-chain, which is split off by the kidney.

Various theoretical objections to the above work have never been experimentally supported. On the other hand, an analogy may be found in the experiments of Embden, who perfused glycogen-free livers with blood, and concluded that a sugar-forming material existed both in the livers and in the blood. But the perfusion experiments, which are the ones criticized, are perhaps less weighty than the evisceration experiments, concerning which less is said. The ordinary mechanism of sugar-production is seriously disabled in these experiments; and the excretion of sugar in quantity exceeding that in the blood furnishes some degree of evidence in favor of the Pavy doctrine.

The experiments of Teissier, Sarvonat and Rebattu, who claimed that small glycogen injections increase the glycosuria from small phloridzin injections, were mentioned in Chapter II.

Loewi (1*A*) was one of the first to suggest that the phloridzin-kidney splits a sugar-compound. Loewi and Neubauer, confirmed by Glaessner and Pick (1), found that diuretics do not increase phloridzin glycosuria. As previously mentioned, in

forms of glycosuria known to be due to excretion of the blood-sugar, this excretion is regularly increased by diuretics. The unique position of phloridzin in this respect may well be interpreted in favor of a unique mechanism. The same unique position is shown in the work of Nishi (3). By separate analyses of the two portions of the kidney under various conditions, he found that in other types of glycosuria the sugar-content of both medulla and cortex, especially of the cortex, is increased. In phloridzin glycosuria the kidney contains less sugar than in other forms, and the medulla contains more than the cortex. Nishi concludes that sugar excretion in phloridzin poisoning occurs in the renal canaliculi, as opposed to other forms, in which excretion occurs in the glomeruli.

Lepine [(1), p. 274 ff] outlines his findings that in phloridzin poisoning, the blood of the renal vein contains more dextrose than the arterial blood. In his paper (5) he answers the criticisms of Erlandsen. Lepine [(1), p. 277] makes the point that in clinical levulosuria, phloridzin causes the patient to excrete dextrose, not levulose.

In the experiments of Winifred C. Cullis, frogs' kidneys were perfused with Locke solution containing various substances. Other diuretics caused no glycosuria. But when a phloridzin solution was perfused, the urine contained a reducing substance. The omission to identify this substance as dextrose is unfortunate; but in view of other known facts, it is probably safe to assume that the substance was dextrose. If so, this dextrose was not derivable from preformed dextrose in the kidney, nor from the sugar-free perfusion fluid, and was therefore necessarily produced in the kidney. The occasional excretion of reducing substance during saline perfusions has been noted by other authors, *e.g.*, Nishi (3); but it is no such constant phenomenon as described in the above experiments, which also were checked up by suitable controls.

EXPERIMENTS.

My experiments have included (1) alterations of renal permeability; (2) phloridzin experiments. They have dealt chiefly with the relation of renal forms of glycosuria to diabetes.

1. Alterations of Renal Permeability.

It was found in previous chapters that the non-diabetic kidney excretes only a small proportion of dextrose, no matter how large

the dose; on the other hand the diabetic kidney excretes dextrose very freely. The difference was attributed to a different state of dextrose in the two cases. A possible slight objection might still be raised, to the effect that some toxic substance may be present in diabetes, which renders the kidney more permeable to sugar. Experiments were therefore performed to test the behavior when permeability is altered.

CAT 53.

Male, maltese; weight 4200g.
Diet 200g. lean meat.

Date	Subcutaneous Injection	Glycosuria
Dec. 1	100cc. 10% dextrose solution.	0
" 3	20cc. 10% dextrose solution containing 2g. NaCl.	0
" 5	50cc. 10% dextrose solution containing 5g. NaCl.	0.8% (1.63g.)
" 8	50cc. 10% dextrose solution left side, and 50cc. 10% NaCl solution right side.	Slight
" 16	50cc. 10% dextrose solution.	0

There was the usual marked diuretic action of the NaCl in each instance. It is evident that the salt produced a decided lowering of tolerance, whether given with the sugar or on the opposite side of the body. Glycosuria resulted in each case when the dose was half that which was assimilated perfectly on December 1. But the dosage on December 3 was too small to produce glycosuria.

CAT 50.

Female, mottled; weight 2800-3100g.
Diet 200g. lean meat.

Date	Subcutaneous Injection	Glycosuria
Oct. 20	100cc. 10% dextrose solution.	0.9% (0.675g.)
" 26	50cc. 10% dextrose solution.	0
Nov. 2	50cc. 10% dextrose solution right side, and 50cc. 10% saccharose solution right side.	7.5% (6.75g.)
" 5	150cc. 10% dextrose solution.	1.8% (2.88g.)

Here it is seen that saccharose acts powerfully in lowering the tolerance for dextrose. On October 26, 5 g. dextrose subcu-

taneously produced no glycosuria. On November 2, the same dose with 5 g. saccharose caused heavy glycosuria. This glycosuria was far heavier and of longer duration than that which followed the injection of 15 g. dextrose (*i.e.*, three times the previous dose) on November 5. Saccharose alone never causes excretion of reducing sugar in cats.

RABBIT 32.

Male; weight 2 kilos.
Catheterized 10.30 A.M. and 5 P.M. daily.
Measured water supplied ad libitum.

Date	Treatment	Water cc.	Urine cc.	Glycosuria
Apr. 16	*24 hours starvation.	20	5 P.M. 8	0
" 17		25	10.30 A.M. 30	0
May 7	24 hours starvation. Subcut.injection 15cc. 80% dextrose solution.	55	5 P.M. 6	0
" 8		60	10.30 A.M. 26	0
" 16	24 hours starvation. Subcut.injection 15cc. 80% dextrose solution left side, 15cc. 10% NaCl solu.right side.	130	5 P.M. 14	9.73%
" 17		45	10.30 A.M. 10	1.46%
" 21	24 hours starvation. Subcut.injection 15cc. 10% NaCl solution.	75	5 P.M. 65	0
" 22		55	10.30 A.M. 54	0
" 31	24 hours starvation.	40	5 P.M. 32	0
June 1		20	10.30 A.M. 60	0

*Each starvation period began at 10.30 A.M., after catheterizing. The quantities of water and urine on the day following are for the 5 P.M. - 10.30 A.M. period.

Here the plan of comparison between fast-days was employed. April 16 and May 31 were used as control fast-days.

May 7, dextrose subcutaneously diminished the urine even though the drinking was increased; *i.e.*, the usual well-marked anti-diuretic effect was present.

May 21, NaCl subcutaneously proved itself a diuretic as usual.

May 16, the two injections were combined. Here we see that the same dose of dextrose, which on May 7 produced no glycosuria,

now produces a glycosuria of 9.73 per cent. But at the same time, the diuresis ordinarily resulting from NaCl was abolished by the dextrose.

This is the important point. There is no good reason to assume that in diabetes mellitus a toxic or diuretic substance is present which renders the kidneys more permeable for sugar. The assumption can be positively ruled out by the test of diuresis. There are many substances, including NaCl and diuretics in general, which increase the permeability to dextrose. *But there is no such substance which causes dextrose to act as a diuretic.* In diabetes mellitus, dextrose is an active diuretic. In cases of mere alteration of renal permeability, dextrose remains an anti-diuretic. Conditions in diabetes mellitus therefore cannot be explained on the assumption of a diuretic or toxic substance which increases the permeability of the kidney to dextrose.

2. Phloridzin Experiments.

The phloridzin experiments were performed primarily from the standpoint of diabetes mellitus; but at the same time, the opportunity seemed favorable to contribute a little to the question of the mechanism of phloridzin glycosuria. Difficulties were encountered, partly because of distemper in the laboratory. For this reason, the experiments to be presented are not as numerous as desired, and in some cases exact controls are lacking. The details concerning which error is possible are discussed later. The desired facts concerning phloridzin glycosuria in relation to diabetes were established fully and unequivocally.

Mention has already been made that certain authors once supposed that phloridzin splits off free sugar from the blood-jecorin. Loewi's idea, that the phloridzin-kidney sets free the combined sugar of the blood, is a different conception. But since we have in phloridzin poisoning a condition in which sugar seems to flow with abnormal readiness through the kidney, when present in normal or even reduced quantity in the blood, the question naturally arises whether this condition can be explained on the basis of a "free" state of the circulating sugar. In diabetes the circulating sugar is free. Is the phloridzin condition perhaps similar?

To answer this question, the characteristic tests of diabetes must be applied to phloridzin glycosuria. These tests pertain to excretion of sugar, water, and nitrogen. The best method has

appeared to be to feed phloridzin. The reasons for choosing this method have been:

(1) It is not necessary to deal with maximally phloridzinized animals. All that is necessary is that the animal shall be constantly excreting sugar. The question is simply, does this sugar-excretion occur because dextrose circulates in "free" condition, or because the kidney is abnormally permeable, or for some other reason?

(2) Subcutaneous injections of phloridzin must be frequently repeated, or the glycosuria cannot be kept uniform. But by feeding phloridzin once or twice daily, the slower absorption results in a fairly uniform glycosuria throughout the twenty-four hours.

(3) Possible risks concerning the nitrogen excretion are avoided by the feeding method.

Two such series of experiments were performed. The principal data may be tabulated as follows.

TABLE I. DOG 21.

Diet 225g. Bread-and-Meat Mixture at 4.30 P.M.
Measured water ad libitum.
Phloridzin 7g. daily by stomach-tube.

Date	Hour	Treatment	Water	Urine		
				Quant.	Reducing Sugar	
				cc.	%	g.
July 8	9.30			150	7.3	10.95
	1.P.M.			110	4.05	4.455
	4.30			42	9.1	3.822
	5.		85			
	8.		55			
July 9	9.30	Subcut.injection of 70cc. 80% dextrose(8g. per kilo).		162	8.1	13.122
	11.		60			
	12.		75			
	1.P.M.		75	52	10.4	5.408
	3.30		245			
	4.30			65	13.3	8.645
	9.		300			
July 10	9.30		25	300	4.6	13.8
	1 P.M.		225	145	3.6	5.22
	4.30			50	7.3	3.65
	8.		65			
July 11	9.30			175	1.5	2.625
	1.P.M.			50	7.3	3.65
	4.30		150	35	7.3	2.555
	8.30		140			
July 12	9.30	Subcut.injection of 56g. saccharose in 70% solu. (8g. per kilo).		130	2.1	2.73
	11.		210			
	12.		250			
	1.P.M.			180	3.0	5.4
	4.30		250	125	3.0	3.75
	11.		315			
July 13	9.30			285	1.6	4.56
	1.P.M.			200	4.0	8.
	4.30			34	6.6	2.244

TABLE II. DOG 18.

Diet 275g. Bread-and-Meat Mixture, at 5 P. M.
Water 300cc. by tube morning and evening.
Phloridzin 7g. daily by stomach tube.

Date	Hour	Treatment	Urine			
			Quant. cc.	Sugar %	Sugar g.	Nitrogen g.
Apr. 4	9.30	Phloridzin begun.	260	---	---	4.
	5.P.M.		360	2	7.2	1.48
" 5	9.30		200	2.3	4.6	2.955
	5 P.M.		390	1.6	6.24	1.84
" 6	9.30	Subcut. injection 40.1cc. 80% dextrose (4g. per kilo).	220	2.5	5.5	3.014
	1.P.M.		140	2.7	3.78	
	5.P.M.		70	7.3	5.11	*1.71
" 7	9.30		255	4.6	11.73	2.16
	1.P.M.		235	2.6	6.11	
	5.P.M.		70	2.8	1.96	*1.63
" 8	9.30		290	3.2	9.28	2.6
	5.P.M.		270	1.3	3.51	1.39
" 9	9.30	65.7g. dextrose by stomach tube (8g. per kilo).	310	2.6	8.06	3.53
	1.P.M.		70	4.8	3.36	
	5.P.M.		90	8	7.2	*1.52
" 10	9.30		380	4.3	16.34	3.47
	1.P.M.		150	2.3	3.45	
	5.P.M.		45	6.6	2.97	*0.83
" 11	9.30		180	2.6	4.68	3.74
	1.P.M.		260	0.94	2.632	
	5.P.M.		60	4.3	2.58	*1.35
" 12	9.30		280	5.2	14.56	3.21
	1.P.M.		260	1.3	3.38	0.467
	5.P.M.		60	6.6	3.96	0.39
" 13	9.30	Intravenous injection of 32.5cc. 25% dextrose (1g. per kilo).	230	5.2	11.96	4.42
	1.P.M.		150	2.3	3.45	0.489
	5.P.M.		110	2.1	2.31	0.649
" 14	9.30		270	1.7	4.59	4.49
	1.P.M.		280	1.1	3.08	
	5.P.M.		80	6.8	5.44	1.48
" 15	9.30	Subcut. injection of 82cc. 80% dextrose (8g. per kilo).	160	2.6	4.16	3.38
	1.P.M.		170	2.8	4.76	
	5.P.M.		60	9.1	5.46	*1.31
" 16	9.30		170	4.3	7.31	3.46
	1.P.M.		285	1.5	4.275	
	5.P.M.		142	6.1	8.662	*3.38
" 17	9.30	Intravenous injection of 98.5cc. 25% dextrose.	280	1.7	4.76	4.2
	1.P.M.		320	2.3	7.36	0.82
	5.P.M.		150	5.	7.5	0.42
" 18	9.30		320	4.	12.8	3.97
	1.P.M.		130	2.	2.6	0.818
	5.P.M.		80	5.2	4.16	0.8
" 19	9.30	Phloridzin stopped.	350	4.8	16.8	5.21
	5.P.M.		265	Faint	---	1.4
" 20	9.30		380	---	---	2.98

*Total for Urine of 1 and 5 P.M.

Summary for Dogs 21 and 18.

First will be considered the facts established in comparison with diabetes mellitus.

In phloridzin poisoning, dextrose given subcutaneously or orally is an anti-diuretic, just as in normal animals. This is shown by the diminution of urine when Dog 21 received 8 g. per kilo subcutaneously on July 9, with compensatory polyuria on July 10; likewise when Dog 18 received 4 g. per kilo subcutaneously on April 6; likewise when Dog 18 received 8 g. per kilo by mouth on April 9; likewise when Dog 18 received 8 g. per kilo subcutaneously on April 15. In this last instance, the secondary polyuria does not begin till after the morning catheterization on April 16. The diminution of urine after dextrose injection is shown not only on fixed water-supply, but also, as in Dog 21 on July 9, when water is supplied *ad libitum*.

In phloridzinized animals, dextrose shows its usual diuretic activity when given intravenously. The case of Dog 18 on April 13 is an exception. Likewise, saccharose is unchanged as respects diuresis.

With a liberal diet supplying plenty of carbohydrate, dextrose given by any route has essentially the same effect upon the nitrogen excretion in phloridzinized as in normal animals. This is shown by the oral, subcutaneous, and intravenous tests in Dog 18. Any slight irregularities can be accounted for by the diarrhea of the phloridzinized dog. Under conditions of carbohydrate deficiency, dextrose is known to spare nitrogen in phloridzin poisoning. The important point is that dextrose does not produce in the phloridzinized animal that notable increase of nitrogen output which it produces in the diabetic animal.

Moreover, the paradoxical law of dextrose holds good in phloridzin poisoning just as in all other non-diabetic conditions. When these two dogs received dextrose by any route, they excreted a greater quantity than normal dogs, but they assimilated most of the dose nevertheless. The working of the law is seen when Dog 18 on April 6 received 32 g. dextrose subcutaneously; the consequent excretion on that day was 8.89 g. On April 15 the same dog received 65.6 g. dextrose subcutaneously, and the subsequent urines of that day contained 10.22 g. dextrose. In other words, the more sugar is given, the more is assimilated, just as in the normal animal. This rule applies even in the so-called

"maximal" phloridzin poisoning. Reference may be made to the paper of Stiles and Lusk in this connection. The "maximally" phloridzinized dog will excrete quantitatively all sugar up to a certain amount; but any quantity above this dose will be assimilated just as in the normal animal. The impression given is as though some compound in the body of the phloridzinized animal requires saturation with dextrose; this compound is broken up by the kidney and the dextrose excreted; but the power of utilizing dextrose as such is absolutely unchanged, and accordingly any dextrose in excess of the amount required for the hypothetical compound is utilized in normal manner.

This entire behavior is in striking contrast with the conditions in diabetes, where dextrose is an active diuretic, increases the nitrogen output, and (in "total" diabetes) fails to be utilized to the extent of a single molecule. Even in milder diabetes, where there is still some tolerance for dextrose, the more is given the poorer is the assimilation, the rule therefore being the opposite of that in phloridzin glycosuria.

The conclusion is that the proposed tests of diabetes hold good in distinguishing it sharply and unmistakably from phloridzin glycosuria. Dextrose does not circulate in free form in the phloridzinized organism. In phloridzin poisoning, we see the paradox that an animal, which constantly excretes dextrose spontaneously, is at the same time able to utilize injected dextrose; and the quantity utilized increases with the dose injected, just as in the normal animal. The same paradox is seen in every non-diabetic form of glycosuria.

Turning now to the question of the phloridzin mechanism, the data are to be recognized as incomplete, conclusions cannot always be positive, and in some instances a possibility of error exists. The latter possibility arises from the following factors:

(1) Inasmuch as experiments with fresh dogs were spoiled by distemper, it was necessary to use immune animals which had been in the laboratory for a considerable time and had been used for various sugar-injections. The possibility that these animals had suffered changes, especially in renal permeability, must be considered, though not very probable. The atypical behavior of Dog 18 on April 13 must be admitted, but in other tests both dogs seemed to behave normally.

(2) Comparisons of sugar-excretion under given conditions are not conclusive unless a sufficient number of experiments are

done. Variations in the same animal on different occasions introduce a slight possibility of error. Under these limitations, the data bearing upon the phloridzin mechanism may be discussed as follows.

First, as respects the spontaneous phloridzin glycosuria, it does not appear as though the sugar acts as a diuretic. This statement has reference to the debate as to whether phloridzin is a "primary" diuretic, or whether the diuresis is "secondary" and due to the excreted sugar, which prevents resorption of water in the renal tubules. In these records, wherever the relations are undisturbed by injections, it will be seen that the morning specimen of urine is generally the greater, but its dextrose percentage is less; the evening specimen is smaller in volume, but the dextrose percentage is higher. The same quantity of water is given morning and evening; but the phloridzin is given mornings, and the feed always given evenings; the impression is as though the usual increase of urine followed feeding, without any relation to either phloridzin or glycosuria. It is, however, not my intention to participate in the debate on this question. Attention should be called to the fact, that my demonstration of the anti-diuretic action of dextrose in phloridzin-poisoning, as in other conditions, has no positive bearing upon Loewi's contention that phloridzin-diuresis is due to dextrose. In these phloridzinized animals, the greater part of the injected dextrose circulates in its normal combined form and is assimilated; it therefore inevitably follows the same laws as in normal animals. But the glycosuria resulting from phloridzin is not like a dextrose injection. It is supposedly a production of dextrose in the kidney, the splitting off of dextrose from some larger molecule or complex. Whether the dextrose thus abnormally split off may have a diuretic tendency, by preventing resorption of water in the renal tubules, is a question which stands by itself, and has no relation to the behavior of dextrose circulating in normal combination. Nevertheless, the non-parallelism between glycosuria and diuresis speaks somewhat against the view that the sugar acts as a diuretic.

The question of the supposed increased permeability of the kidney may next be considered, first on the basis of the saccharose experiments. On July 12, Dog 21 received a subcutaneous injection of 8 g. saccharose per kilo. The quantities of urine and reducing sugar are shown in the table. The percentages of saccharose were as follows: 1 p.m., 7.1 per cent; 4:30 p.m.,

12.2 per cent; July 13, 9:30 a.m. 6.4 per cent; 1 p.m., 1.8 per cent; 4:30 p.m., 3.2 per cent; July 14, 9:30 a.m., 0.2 per cent. The total saccharose excreted was 51.298 g., about the same as might be expected in a normal dog. General experience indicates that there was no acceleration of excretion in this case; but the rate of absorption might be important. Intravenous injection is more suitable, and the results in Dog 21 may be compared on June 27 without phloridzin, and on July 3 with phloridzin. The injection in each case was 100 cc. 25 per cent saccharose solution.

TABLE III.

Hour	June 27 (without phloridzin)			July 3 (with phloridzin)		
	Urine			Urine		
	Quant. cc.	Dextrose %	Saccharose %	Quant. cc.	Dextrose %	Saccharose %
9.30–9.45 A.M. Injection						
11 A.M.	150	0.48	9.3	175	1.4	7.6
12 M.	90	0.53	6.76	70	2.6	6.8
1 P.M.	50	0.34	2.67	37	3.3	4.8
2 P.M.	52	0.21	0.65	21	7.1	1.0
3 P.M.	35	0.1	0.32	15	7.3	1.3
4 P.M.				12	7.3	2.1
4.30 P.M.	20	0	0	7	4.8	1.1
5.45 P.M.				18	7.7	0.4
8 P.M.				33	9.1	0

The reducing sugar in each case was reckoned as dextrose. The qualitative and quantitative tests of saccharose showed an earlier termination of excretion on June 27 without phloridzin than on July 3 with phloridzin. The rule cannot be accepted as general on the basis of one experiment. This finding with saccharose agrees with that of Spiro and Vogt with levulose. It differs from their results with saccharose. One point at least is definitely proved, *i.e.*, saccharose does not show any specific tendency to inhibit or diminish phloridzin glycosuria. The effect upon the quantity of dextrose excreted may be expressed as follows, the figures indicating the "day-time" total, from 9:30 a.m. to 4:30 p.m.

	Dextrose excretion, grams.
July 2	10.04
July 3, intravenous saccharose injection	8.413
July 4	8.85
July 10	8.87
July 11	6.205
July 12, subcutaneous saccharose injection	9.15

Whether the dextrose output is increased or decreased after saccharose injection seems therefore to be accidental. The result is in striking contrast to the previous finding in Cat 50, where the permeability of the kidney for dextrose (as such) was found to be so markedly increased by saccharose.

Further experiments along these lines with a variety of sugars seem desirable.

Some of the relations regarding the excretion of dextrose itself may next be noticed. On July 9, Dog 21 received a subcutaneous injection of 8 g. dextrose per kilo. In a normal animal, this dose would be just on the border-line of tolerance. The result in this case was an excretion of 14.053 g. dextrose in the 1 p.m. and 4:30 p.m. urine, as compared with 8.277 g. on the day preceding (July 8), and 8.87 g. on the day following (July 10). This means a net increase of some 6 g. dextrose over and above the excretion produced by the phloridzin alone or by the dextrose injection alone. The result is fully in accord with the uniform findings, as by Huot and by Erlandsen, of the increase of phloridzin glycosuria resulting from hyperglycemia. But it does not enable us to choose between the two theories concerning the phloridzin mechanism.

On April 6, Dog 18 received a subcutaneous injection of 4 g. dextrose per kilo, which would have caused no glycosuria in a normal dog. The dextrose excretion up to 5 p.m. was 8.89 g., as compared with 7.176 g. the day before. On the following day, with secondary polyuria, the dextrose excretion in the 1 p.m. and 5 p.m. specimens was 8.07 g.

On April 15, Dog 18 received 8 g. dextrose per kilo subcutaneously. The dextrose output in the 1 p.m. and 5 p.m. urines was 10.22 g. On the preceding day (April 14) it was 8.52 g., and on the following day (April 16) it was 12.937 g. From examples of this sort it may be inferred that the increase of phloridzin glyco-

suria is merely a matter of available carbohydrate, and not the result of hyperglycemia *per se*. This view will be found confirmed in the experiments with intravenous injection in Dog 21, on July 6 with phloridzin, and on August 4 without phloridzin. On each of these days, 100 cc. 25 per cent dextrose solution was injected intravenously. The results may be compared in table form as follows.

TABLE IV.

Hour	July 6 (with phloridzin) Urine		Aug. 4 (without phloridzin) Urine	
	Quant. cc.	Sugar %	Quant. cc.	Sugar %
9.45-10 A.M. Injection				
11 A.M.	150	5.2	150	4.6
12 M.	23	12.2	53	3.2
1 P.M.	11	8.1	10	1.1
2 P.M.	15	7.3	15	Slight
3 P.M.	15	10.4	52	Faint
4.30 P.M.	15	9.1	33	Neg.
	Total 229		Total 313	

Here the first urine-specimens (11 a.m.) happen to be equal. The sugar-percentage is naturally higher on the phloridzin day, but the difference is suspiciously slight. Part of the glycosuria must be attributed to phloridzin. The record of Dog 21 shows that the sugar-percentage from phloridzin was always high. The lowest value that can be chosen is 1.4 per cent on July 3, in a urine-specimen of 175 cc., after intravenous injection of saccharose. If 1.4 per cent be subtracted from 5.2 per cent, or in any other way a reasonable allowance be made for the glycosuria due to phloridzin alone, the result would seem to indicate that the glycosuria due solely to the injected sugar is less with phloridzin than without. Such a calculation, if valid, implies that phloridzin diminishes instead of increasing the permeability of the kidney for dextrose as such. On any basis, these figures are hard to reconcile with any idea of either active or passive increase of renal permeability. It might be argued that the stimulated kidney is "satisfied" by a percentage of 5.2 per cent. But it should be noted, that in all the succeeding specimens the percentage is much

higher than this; frequently double. Rosenfeld (7) states that hyperglycemia disappears in phloridzinized animals within four hours after an intravenous dextrose injection. At any rate, it is certain that the blood-sugar is less in the later than in the earlier hours. And by catheterizing every hour, it becomes evident that the percentage of sugar in the urine bears no possible relation to the percentage of sugar in the blood. Again the fact is hard to reconcile with any simple increase of permeability, active or passive.

Similar relations hold for the experiment with Dog 18 on April 17 (Table II). In order that there might be no lack of water, this dog received 600 cc. per day by tube, in addition to 200 cc. with the feed. On this date, at 9 a.m., an intravenous injection of 98.5 cc. 25 per cent dextrose solution was given. There was the usual diuresis. In the four hours from 9 a.m. to 1 p.m., it is presumable that hyperglycemia was present at least part of the time. In the four hours from 1 to 5 p.m., there was presumably little or no hyperglycemia. It is noteworthy, then, that in the latter four hours, not only was the percentage of sugar in the urine more than twice as high as in the earlier four hours, but also the absolute quantity of excreted sugar was greater (7.5 g. against 7.36 g.).

It is also possible to make comparisons between the effects of dextrose injection and the effects of feeding. The regular evening meal of Dog 18 contained much carbohydrate, but obviously would not produce much hyperglycemia. The above-mentioned intravenous injection of April 17 resulted in a total "daytime" excretion of 14.86 g. dextrose. During the following night, *i.e.*, after feeding, the excretion amounted to 12.8 g. During the next night (April 18–19) it amounted to 16.8 g. During the night of April 11–12, it amounted to 14.56 g. These are the highest values for night-urine, but so also is April 17 the highest for day-urine. The fact that a meal of bread may produce nearly equal (April 17–18, April 11–12) or even superior (April 18–19) sugar-excretion, is one reason for believing that a dextrose injection increases phloridzin glycosuria through some other mechanism than mere hyperglycemia. Incidentally, it may be observed that when dextrose was fed on April 9, the urine during the day showed an increased dextrose percentage; but the actual excretion was only 10.56 g., as opposed to 16.34 g. in the night-urine (April 9–10).

The findings with subcutaneous injection are to the same effect. When dextrose is injected subcutaneously in the moder-

ate doses employed here, at 9 or 9:30 a.m., it is presumable that hyperglycemia is greater during the earlier than during the later part of the day. But glancing down the first tables presented, for Dogs 18 and 21, it is evident that whenever dextrose was thus injected, the percentage of sugar in the 5 p.m. urine was always greater than in the 1 p.m. urine. Authors in the past have found apparent support for the theory of increased permeability, in experiments showing that dextrose injections increase phloridzin glycosuria. But they did not take the trouble to collect the urine at sufficiently short intervals. Had they done so, they would have found, as here, that parallelism between the blood-sugar and the urine-sugar is lacking.

It is recognized that a number of objections may be raised against the conclusiveness of these experiments. For reasons mentioned, the research was dropped unfinished, after the relations with diabetes had been established. But two points seem to stand out rather prominently nevertheless. (1) The lack of parallelism between blood-sugar and urine-sugar. It seems probable that analyses of the blood and urine at suitable intervals would substantiate this lack of parallelism, and might likewise demonstrate that greater glycosuria results from a large feeding of bread or meat than from a small dextrose injection, though the latter may produce greater hyperglycemia. (2) The contrast between phloridzin and substances which actually increase renal permeability. Under the previous heading (increase of renal permeability) it was seen how powerfully saccharose and NaCl increase the excretion of injected dextrose. These substances themselves do not cause glycosuria. If phloridzin acts by increasing renal permeability, it must be more powerful in this respect than saccharose or NaCl. But the experiments with dextrose injections do not harmonize with such a view.

In general, the impression is received that dextrose injections increase phloridzin glycosuria not by hyperglycemia per se, but rather by increasing the supply of readily available carbohydrate.

CONCLUSIONS.

I.

Concerning the phloridzin mechanism, it is suggested that so far as present evidence goes, the idea of a simple (active or passive) increase of renal permeability seems less probable than

the other hypothesis, that the kidney derives the sugar from some larger molecule or complex. The nature of the hypothetical substance is as yet unknown. The doctrine of Pavy, Lepine, and others, that the excreted dextrose is derived from protein, "virtual" sugar, or some substance other than dextrose itself, is supported by the following evidence.

1. The analyses which claim to show a greater quantity of dextrose in the urine and the blood of the renal vein than in the blood of the renal artery.

2. The production of glycosuria after exclusion of viscera, involving excretion of more sugar than contained in the blood.

3. The experiments in which excised kidneys formed a reducing substance when perfused with sugar-free fluid containing phloridzin.

4. The calculation of Erlandsen, that derivation of the urine-sugar from the blood-sugar would involve complete sugar-freedom of the blood of the renal vein.

These facts or the interpretation of them are questioned by many, and in the course of time this view has probably lost rather than gained in strength. The subject is still very doubtful, and it cannot be said that we know from what source the excreted sugar is derived. But with regard to the broad general question, the best evidence at present seems to stand somewhat against the view that the glycosuria represents a simple (active or passive) increase of renal permeability to the ordinary blood-sugar, and in favor of the general view that the excreted sugar is derived from some sort of compound or complex, which might be a large molecule, or perhaps an abnormal blood-sugar combination, in which phloridzin itself might conceivably be a component. The evidence favoring this general hypothesis may be summarized as follows.

1. The possible analogy with the mellituria produced by glycogen, dextrin, etc. (Chapter II.)

2. The effects of diuresis. All glycosurias known to depend upon passage of blood-sugar into the urine are increased by diuresis. Phloridzin stands out in contrast.

3. The diminution of permeability of the phloridzinized kidney for levulose, perhaps also for saccharose and other sugars.

4. The apparent lack of parallelism between hyperglycemia and glycosuria. The contrast in this respect between phloridzin and substances which are known to increase renal permeability.

5. The D/N ratio. Phloridzin cannot be considered a very powerful agent of primary sugar-production. Much of the sugar-production may be considered secondary. The theory of increased permeability therefore does not explain satisfactorily why the ratio should be higher in phloridzin poisoning than in diabetes. The different ratio seems best explainable on the supposition of some radically different mechanism.

6. The remarkable quantitative relations in phloridzin poisoning. The assumption of a combination, requiring a more or less fixed quantity of sugar for its saturation, readily explains the fact that a given dose of phloridzin poisons only for a given dose of sugar-forming material, also Ringer's observation that sugar spares protein even when the sugar itself is quantitatively excreted. The idea of a simple change of renal permeability seems less suited to explain these quantitative relations.

II.

The only positive conclusion, which it was the purpose of these experiments to establish, concerns the relations of diabetes mellitus and phloridzin glycosuria. The paradoxical law and diuretic action of dextrose distinguish sharply and decisively between these fundamentally different conditions.

CHAPTER XVI.

ADRENALIN.

ADRENALIN is an animal alkaloid produced by the medullary portion of the adrenal gland. The discussion of the influence of adrenalin upon the carbohydrate metabolism requires a brief preliminary description of the adrenal gland, adrenalin itself, and other physiological effects of adrenalin. The best general accounts of this subject are given by Biedl (3) and in the referat of Bayer (2), as also that of Swale Vincent on internal secretion.

1. The Adrenal Organs.

The adrenal glands of man and other mammals consist of two distinct parts, cortex and medulla, which represent separate organs. In birds the two portions are not thus separate, and the adrenals are composed of interwoven cords of the two types of cells. In reptiles the arrangement is somewhat similar, with a smaller proportion of medullary substance. In amphibia the two types of tissue begin to be spread out and separated, and in fishes the two are entirely independent, being scattered in the form of small nodules and clumps of cells over a considerable area in and about the kidneys. In comparative anatomy, the two organs receive distinctive names: one, the INTERRENAL SYSTEM, corresponds to the mammalian adrenal cortex; the other, the CHROMAFFIN SYSTEM, corresponds to the mammalian adrenal medulla. Although differing in anatomical relations, these two organs or systems preserve the same histological and chemical characteristics throughout all classes of vertebrates.

A. INTERRENAL SYSTEM.

This tissue is of mesodermal origin, derived from proliferation of the peritoneal epithelium. All are familiar with its adult structure in the human adrenal cortex, consisting of polygonal or rounded cells in nests and columns, arranged in three "zones," which from without inward are named the glomerular, fascicular, and reticular. Small accessory bodies ("accessory adrenals")

belonging to this system are common, varying in frequency according to the species of animal. The most common locations are about the adrenals, the kidneys, and the sexual organs (broad ligament in female; spermatic cord, pampiniform plexus, testis and epididymis in male). The distinguishing characteristic of the interrenal system throughout all vertebrates is the presence of numerous lipoid granules in the cells. These are not seen in ordinary preparations, for they are removed by such fat-solvents as xylol, ether, alcohol, etc. They do not take the ordinary protoplasmic stains, but are colored vividly by fat-stains. They do not however consist of true fat. They show double refraction, hence belong among the bodies called "liquid crystals." The idea that they are composed largely of lecithin has proved incorrect, and they are now supposed to consist chiefly of cholesterin esters and sphingomyelin. The adrenal ranks as one of the richest in lipoids among the organs of the body; more than a third of the total dried weight is lipoid. The most recent study is that of Mayer, Mulon and Schaeffer, who distinguish different animal species as possessing a "fat" or "lean" adrenal cortex. In addition to lipoid granules, the cortical cells contain pigment, and Altmann's fuchsinophile granules. Neither the lipoids nor the pigment are believed to represent secretion. The function of the interrenal system is entirely unknown. Guesses have been made that it produces cholin as an antagonist to adrenalin, that it distoxicates poisonous substances, and that it assists in the manufacture of adrenalin. The first and third at least are improbable. In some manner, the interrenal system is necessary to life. Animals such as rats and rabbits may survive removal of both adrenal glands, if accessory adrenals, consisting of cortical substance, are present. Biedl found that seven-eighths of the adrenal-gland tissue may be safely removed, provided the remaining one-eighth consists of cortex. In fishes suitable for such an operation, he was able to prove that extirpation of the interrenal system, leaving the chromaffin system intact, results regularly in death within about three weeks, the only symptom being progressive weakness.

B. Chromaffin System.

This system is of ectodermal origin, derived from the same cells that produce the sympathetic ganglia. Its intimate and important relation with the sympathetic nervous system is therefore

not surprising. The cells of the chromaffin system are distinguished by the brown stain imparted to them by chrome-salts. This stain indicates adrenalin-content of the cells, and it varies according to the richness of this content. A similar staining reaction is given by certain cells in a few invertebrates which produce adrenalin. The chromaffin cells which compose the medulla of the human adrenal are rounded or polygonal, finely granular, and arranged in irregular balls and cords. Other such cells are present in the paraganglia sometimes found near the adrenals, in the carotid gland, in all sympathetic ganglia, in many nerve-plexuses, and scattered in various places along sympathetic fibres and nerve-cells, so that Biedl estimates that this *free* portion of the chromaffin system outbulks the portion contained in the adrenal medulla. The chromaffin system is doubtless essential to life. The reason why animals can live after epinephrectomy if a sufficient quantity of interrenal tissue is retained, is that the extensive *free* portion of the chromaffin system is still present and functionating. Operative removal of this entire system is of course impossible. Attempts to destroy the system by specific anti-sera have not succeeded. The one demonstrated function of the cells of this system is the production of adrenalin. It is possible that unknown functions also exist.

Gaskell has lately described the occurrence of chromaffin tissue scattered over most of the body of Petromyzon fluviatilis. The extract showed the typical pressor effect of adrenalin in cats.

C. The Adrenal Glands.

All higher animals possess these paired organs, which consist of most of the interrenal system surrounding a considerable part of the chromaffin system, so as to give at least the impression of a definite organic entity. It is presumed that some purpose is served by this association of the two systems in this manner, but nothing is known concerning it. Many experiments and observations are, however, on record concerning the adrenal glands as individual entities. Understanding that they strictly represent portions of two organs welded together, it is still desirable to know what importance attaches to the adrenal glands as such.

Brown-Sequard first proved that removal of these glands causes death in experimental animals; after years of dispute, his belief has been fully confirmed. Long anæsthesia and severity

of operation hasten death, and to them, and not to absence of adrenalin, is due the rapid fall in blood-pressure and sudden collapse recorded by a number of experimenters. These accidental factors, and the presence of accessory adrenals of varying size and number, also account for the different duration of life in different instances. Operative methods or other avoidable factors also probably explain the emaciation and other changes reported by some authors after removal of only one adrenal. As with other paired organs, one member of the pair is able to perform the work of both, and no symptoms follow removal of one. The fact that animals may live in flourishing condition if they retain even a fraction of one adrenal has been mentioned. My own extirpation experiments (Chapter XIX) confirm these findings; of a series of cats and dogs from which one adrenal was removed, not one lost weight or showed any disturbance; and an animal which survived removal of most of the second adrenal (Cat 60) retained perfect strength and flesh.

Biedl removed both adrenals in the manner freest from criticism, by dislocating both so as to lie outside the peritoneum in an easily accessible position. After 3 or 4 days, a simple subcutaneous operation under very brief anæsthesia sufficed for their removal. Such an animal wakes up promptly and appears fully normal in all respects. For as long as one or two days there is full appetite and liveliness. On the second or generally third day, there begins to be seen a diminution of appetite and of liveliness. From this time on, the symptoms of apathy and general weakness increase steadily; the animal eats nothing, and moves as little as possible. Toward the end, prostration is extreme. The animal lies on its belly with paws extended, conscious but too weak to rise. The temperature sinks far below normal. Hypoglycemia is marked. The heart is feeble and irregular. Respiration is increasingly slow and difficult. Death occurs from this progressive general paralysis, or occasionally with a few slight twitchings or convulsions.

These results were obtained by Biedl in dogs, cats, and rabbits. Except by imitating his operative procedure, one cannot hope to duplicate his results. Epinephrectomized animals are highly susceptible to injury from operation, anæsthesia, etc. Probably this is the reason why after removal of both adrenals at one operation, or even by removal of one at a time in laparotomies many days apart, death generally comes much sooner than described

by Biedl. If the laparotomy is quick and easy, the animal will apparently recover in normal fashion, and within a few hours may be strong and lively. But even when the right adrenal had been removed weeks or months before, and thus the final operation was nothing but the very easy and quick removal of the left adrenal, I have never seen dogs or cats survive longer than $2\frac{1}{2}$ days. Reports of animals which live for weeks after epinephrectomy mean either that the extirpation was incomplete, or that accessory adrenals were present. Kahn (5) has recently shown that monkeys survive epinephrectomy for several days in apparently good condition, then die with the usual symptoms.

The presence of discoverable accessory adrenals varies in different species. According to Biedl, such structures in dogs and cats are rare, in guinea-pigs "exceedingly rare" (4 per cent of cases at maximum); in rabbits they exist in 15–20 per cent, and in rats in almost 50 per cent of the animals examined. After extirpation of one or both adrenals, these accessory structures hypertrophy. These facts explain why a considerable number of rabbits may continue to live indefinitely in apparent health after removal of both adrenals, especially if the glands are removed singly, with a considerable period between operations. Dogs and cats rarely possess enough accessory tissue to survive epinephrectomy. Of four goats operated upon by Moore and Purinton, one survived safely, though accessory adrenals were not found at autopsy. The most notable work with epinephrectomy in rats is that of Schwarz. By removing one adrenal, and waiting several weeks for hypertrophy of accessory nodules to occur, he was able to remove the second adrenal and keep his rats in apparent health, but with absence of glycogen in the livers and with other metabolic peculiarities. Kahn and Starkenstein found the loss of liver-glycogen in such rats to be not quite complete. Also, they were able to keep epinephrectomized rabbits indefinitely, with no apparent disturbance of health and no loss of liver glycogen.

None of the symptoms following epinephrectomy are known to be due to lack of adrenalin. Cybulski believed that animals die from fall of blood-pressure and from the general effects of loss of tone of the sympathetic nervous system, because of the absence of adrenalin; and he reported marked temporary benefit from injections of adrenalin in such animals. But Biedl properly makes the criticism that an equal revivifying effect of adrenalin is obtainable in animals moribund from almost any cause. Strehl

and Weiss experimented with removal of one adrenal and clamping the vein of the other. In some such cases — but only in a minority — a fall of blood-pressure occurred, which could be overcome by removing the clamp from the adrenal vein. But while the latter procedure may be considered analogous to an injection of adrenalin, the fall of pressure is not explainable as an adrenalin deficiency. Biedl points out that if it were so, the decline of pressure after epinephrectomy should be progressive; whereas even in the experiments of the above authors, the pressure after a short time always spontaneously returned to normal. Biedl and other investigators have regularly observed normal blood-pressure for two or three days after complete epinephrectomy. Only in the hours preceding death does a progressive decline of blood-pressure become evident, and a similar decline is seen in all moribund animals. Hoskins and McClure have repeated the earlier experiments with more accurate methods. They found that ligation of the adrenal vessels is not followed by any significant change in the blood-pressure within the time in which adrenalin is known to be destroyed in the circulation; the maintenance of pressure could therefore not be due to adrenalin present before the ligation; and they concluded that the normal blood-pressure is not dependent upon a continual secretory activity of the adrenals.

The hypoglycemia, loss of liver glycogen, and other disturbances of the carbohydrate economy are also unrelated to any lack of adrenalin. Animals die with these symptoms after double epinephrectomy, although all the "free" portion of their chromaffin tissue still remains. If a sufficient amount of *interrenal* tissue remains, in the form either of accessory adrenals, or of adrenal cortex left at operation, the animals survive indefinitely without the above disturbances. In epinephrectomized rabbits, the findings of Kahn and Starkenstein regarding liver-glycogen have been mentioned; and Frank and Isaac (2) found no diminution of blood-sugar. The extreme muscular weakness and general depression following epinephrectomy are likewise due to deficiency neither of adrenalin nor of carbohydrate; accordingly there is no experimental basis for the treatment of Addison's disease with carbohydrate-rich diet [Porges (1)] or with adrenalin [Gautrelet]. When, to overcome the hypoglycemia, an epinephrectomized animal receives dextrose injections to the point of glycosuria, there is no effect upon the symptoms or duration of life (my experiments). Numerous attempts to modify the symptoms of

epinephrectomy by the use of adrenalin or the whole adrenal extract have uniformly failed. In particular, Battelli proved that death in an epinephrectomized dog is not prevented nor delayed by continuous intravenous infusion of adrenalin. Battelli and Stern (1) then performed experiments in which continuous cross-transfusion of blood was maintained by carotid anastomosis between a normal and an epinephrectomized dog. The steady decline in the latter animal was not altered under these conditions. No animal survived more than 40 hours, and the vessels, especially of the abdomen, in the epinephrectomized member of the pair were always found gorged with blood, while the body of the normal dog was practically bloodless. That is, the normal animal died by bleeding into the vessels of the epinephrectomized animal; the circulatory strength was maintained in the former, and was lost as usual in the latter. Adrenalin cannot explain the condition.

2. Clinical Adrenal Disturbances.

Clinical observations constituted the basis of all modern study of the adrenals. Although the organs had been mentioned by Eustachius in 1563, and described more fully by later anatomists, their function and importance remained entirely unknown. In 1855, Addison published his description of a morbid symptom-complex in human patients, associated with anatomical lesions of these little-known organs. The symptoms of Addison's disease are, in his own language, "anemia, general languor or debility, remarkable feebleness of the heart's action, irritability of the stomach, and a peculiar change of color in the skin." The pathological change in typical cases is tuberculosis of the adrenals. Atrophy, inflammation, hemorrhage, and malignant disease are less common findings. Addison's belief in the etiological importance of the adrenal lesions has been confirmed by the later studies, which are tending to clear away certain doubts formerly expressed. These doubts were based chiefly upon cases presenting symptoms like Addison's disease, with normal adrenals, and other cases in which extensive destruction of the adrenals may be found, without the usual symptoms. For the production of symptoms, not only the adrenal glands must be considered, but also the chromaffin cells scattered widely throughout the sympathetic system, and perhaps accessory adrenals composed of cortical tissue. In view of these complex conditions, seeming contradictions regarding the pathology of the disease are not surprising.

Adrenal insufficiency, persistent thymus, and general status lymphaticus are rather frequently associated [see Bayer (2), p. 100]. Lack of adrenalin has therefore been suggested as the cause of "thymus death," but without proof or plausibility. Schur and Wiesel attempted to explain other anæsthetic-deaths on the basis of alleged exhaustion of the chromaffin tissues demonstrable after anæsthesia in experimental animals. Kahn (1), Hordrowski, and Shiota repeated the experiments, and found no such exhaustion. Ingier and Schmorl found an actual increase of the adrenalin content of the adrenals in autopsies of patients of the type mentioned. But recently Elliott has found that all ordinary states of anæsthesia, with ether, chloroform, or urethane, in experimental animals, are attended by exhaustion of the adrenal medulla.

Venulet and Dmitrowsky asserted that starvation causes disappearance of chromaffin substance; that the final weakness is due largely to lack of adrenalin, and that injection of adrenalin prolongs life. They also claimed that potassium iodide inhibits adrenalin secretion, and proposed this fact as the explanation of the benefit of potassium iodide in arteriosclerosis. Luksch, on the contrary, found normal staining of chromaffin tissue and normal adrenalin content in the blood of starving animals. Luksch's view is probable, that when adrenal changes occur in advanced starvation, they are the result rather than the cause of the cachexia.

Other morbid conditions associated with the adrenals, such as hemorrhage, inflammation, neoplasm, etc., give rise to no specific symptoms. The adrenal tumors of the kidney are also accompanied by no characteristic adrenal symptoms. Rare instances of supposed hyperadrenalism are mentioned by Cushing (p. 220); here suspicion probably points chiefly to the cortex, the tissue of which is believed by some to stand in relation with the sexual glands, especially the interstitial cells of the testis. Conditions of over-function of the chromaffin tissue, analogous to hyperthyroidism, are unknown or excessively rare; the case reported by Claude and Baudouin is perhaps a genuine example. Chromaffin over-function and excess of adrenalin in the blood have been claimed to exist in diabetes, in exophthalmic goitre, in Bright's disease, in arteriosclerosis, and in other conditions. Any such essential over-function has, however, not yet been demonstrated, and in most cases has been disproved.

Zimmern and Cottenot have lately claimed benefit from X-ray treatment of the adrenals in cases of hypertension; and Moltschanoff has advanced the opinion that the adrenals have a special importance in connection with diphtheria and other infections. A. Marie has found that adrenalin neutralizes tetanus toxin.

3. Production of Adrenalin.

Vulpian in 1856 discovered that the adrenal medulla is colored green by iron chloride, and that the blood of the adrenal vein gives a similar reaction. A number of later histologists then found granules in the medullary cells, and in the blood of the capillaries bordered by these cells; and since these gave the characteristic reaction, they were interpreted as secretory granules extruded by the cells into the blood and there dissolved. The nature and significance of these granules is now undecided. They have been proved not identical with the cell-granules, and they are considered not to have any connection with the secretion of adrenalin. The cell-granules are, however, supposed to be concerned in the production of adrenalin. According to Stoerk and Haberer's idea, the secretion is elaborated in the granules, and spreads from them into the general cytoplasm, which thus takes on an increasing color with chrome-staining. Even the nucleus may to some extent be permeated with adrenalin. At a certain stage, the secretion begins to diffuse into the capillaries. Here it can be seen, in both fresh and stained preparations, in the form of slimy masses, slow in dissolving in the blood-plasma. A loaded cell discharges itself completely, so that the characteristic stain is lost; and then the process of secretion begins again. Ordinarily, different cells are in different stages of secretion at the same time, for the production of adrenalin is continuous.

The secretion of adrenalin and probably other functions of the adrenals stand under control of the nervous system. The first definite research in this direction was that of Biedl (1*A*), who proved that vaso-dilator fibres for the adrenals exist in the splanchnic nerves. He considered the presence of vaso-constrictor fibres also probable. By testing the pressor effect of the blood of the adrenal vein, he came to the conclusion that true secretory nerves governing the formation of adrenalin probably also exist; that the splanchnics may be considered as not only vasomotor but also secretory nerves for the adrenals.

Dreyer by similar experiments arrived at the following confirmatory conclusions. "(1) The active principle of adrenal extract is present in the blood collected from the adrenal vein and constitutes therefore a true internal secretion. (2) The amount of adrenal substance in the adrenal blood as measured by the extent of the physiological effects it is capable of producing is increased by electrical stimulation of the splanchnic nerve below the diaphragm. (3) The increased secretion resulting from splanchnic stimulation is independent of the blood-vascular changes simultaneously provoked."

Ehrmann (*1A*) could find no changes in the output of adrenalin (as measured by his frog-eye method) after injections of either pilocarpin or atropin. But recently, Cannon, Aub and Binger have reported increased adrenalin secretion produced by injection of small doses of nicotin (0.0035–0.0075 g.).

Asher obtained marked and prolonged increase of blood-pressure by electrical stimulation of the splanchnics in suitably prepared animals. He interpreted the results as an increase of adrenalin due to secretory nerves.

Tscheboksaroff made use of the method of comparative pressor effects of the adrenal blood under different conditions. He concluded that the splanchnics are true secretory nerves for the adrenals. Stimulation of these nerves by the induction current increases adrenalin secretion. Section or ligation of the nerves markedly diminishes it. During splanchnic stimulation there is not only increased adrenalin in the blood but also in the chromaffin tissue itself. The vagus has no perceptible influence upon the secretory function of the adrenals. The secretion of adrenalin into the venous blood proceeds uninterruptedly. An injection of 10 cc. of blood from the adrenal vein, into the circulation of another dog with cut vagi, suffices to raise the blood-pressure by 20–40 mm. of mercury. The increased blood-pressure produced by stimulation of a sensory nerve (sciatic) is not attended with any perceptible change in the rate of adrenalin secretion. Injections of atropin 5–15 mg. or pilocarpin 5–10 mg. have no effect on adrenalin secretion. But injection of physostigmin 5 mg. may increase adrenalin secretion.

Wertheimer and Battez (2 and 3) reported that glycosuria still follows the Bernard sugar-puncture, after a dose of atropin sufficient to paralyze the salivary secretory nerves. Though their paper is intended to disprove the existence of glyco-secretory

nerves for the liver, the application to the adrenals is equally clear. The piqûre is generally supposed to act by a nervous effect upon the adrenals. If atropin paralyzes all secretory nerves, then the occurrence of the usual piqûre-effects in full intensity after atropin poisoning indicates that the impulse which reaches the adrenals is not secretory but vaso-motor. But it is not yet proved that nerves governing internal secretion are paralyzed by atropin.

Popielski (2) has presented arguments against the existence of true adrenal secretory fibres in the splanchnic nerves. He has, however, no evidence as weighty as that which supports the existence of such fibres.

Ehrmann (1*A*) discovered adrenalin-production to be independent of changes of blood-pressure produced by diphtheria toxin and other agents.

Trendelenburg reported that lowered blood-pressure, produced by bleeding, causes a great diminution in the quantity of blood flowing from the adrenal vein, but this blood may show an increased adrenalin content, as if the organism were trying to keep up its usual supply of adrenalin. But an increased production of adrenalin, tending to raise the reduced blood-pressure to normal, does not occur.

Nishi (1*A*), on the basis of experiments with diuretin glycosuria, came to the conclusion that stimuli from the central nervous system reach both adrenals solely through the left splanchnic nerve. Herein he differs with other authors.

Watermann and Smit reported that direct electrical stimulation of the adrenal increases the production of adrenalin, supposedly through an action upon the splanchnic fibres. For findings of other authors in this connection, see Bayer [(2), pp. 33–34].

Kahn (2) found changes indicative of exhaustion in the adrenals of rabbits at the height of piqûre glycosuria. Cutting a splanchnic nerve was found to protect the adrenal of that side from such changes, but protection was perfect only on the left side, because the right adrenal is supplied from both splanchnics.

Starkenstein (3) gained results in harmony with those of Kahn. In animals subjected to asphyxia, he found adrenal changes similar to the above. Cutting the left splanchnic protected the left adrenal from such changes, while the right adrenal showed them as usual.

Pende [ref. by Bayer (2), p. 34] is said to have found that section of the splanchnics is followed by atrophy of the adrenal

medulla. But Shiota failed to produce any effect upon the adrenal structure or adrenalin content by severing everything except the blood-vessels, and he therefore concluded that adrenalin secretion must be largely independent of nerves.

Elliott has proved that the two adrenals normally contain equal amounts of adrenalin, that they can be exhausted by various conditions, including excitation of afferent nerves such as the sciatic or direct injury of the brain, and that section of the splanchnics prevents such exhaustion. Faradization of the splanchnic nerves causes a discharge of adrenalin.

O'Connor (2) found that after division of the splanchnics the adrenalin secretion in the adrenals is greatly diminished or abolished. He concluded that the secretion must be due to a continuous nervous stimulation; but whether this stimulus and rate of secretion, as determined in experiments, are normal or abnormal, was left undecided.

Stewart (3) observed that serum from the adrenal veins of dogs collected during massage of the adrenal gave a positive reaction for adrenalin; before and after the massage the reaction was negative. The serum obtained when no precautions were taken against disturbing the adrenals gave sometimes positive, sometimes negative reactions; when such precautions were taken, positive reactions were obtained only during stimulation of the splanchnic nerves.

Janeway and Park on the contrary hold that the blood of the adrenal vein always contains adrenalin in demonstrable quantity.

We may form the general conclusion that adrenalin is a secretion produced in liquid form by the cells of the chromaffin system, and excreted by them into the blood-vessels. The secretion is under the control of both splanchnic nerves, especially the left; and these nerves contain secretory as well as vaso-motor fibres for the adrenals. The chromaffin system does not govern blood-pressure. The nervous system governs blood-pressure, and adrenalin is not the only agent for the purpose. This latter statement is proved by the normal blood-pressure which may exist for several days after epinephrectomy, by Tscheboksaroff's observation that no increase of adrenalin accompanies the elevation of blood-pressure following sciatic stimulation, by Trendelenburg's finding that lowered blood-pressure produces no tendency to compensatory increase of adrenalin production, and by the experiments of Hoskins and McClure.

4. Effects of Adrenalin on Various Tissues and Organs.

Earlier writers disputed the specific effects of extracts of the adrenals, and attributed the resulting physiological phenomena to putrefactive or other products, infection, etc. Oliver and Schaefer in 1894 discovered the specific blood-pressure-raising property of this extract, and the same finding was later announced independently by Cybulski and by Szymonowicz. Since then it has been the object of a host of researches. The typical effects are seen only after intravenous injection.

Adrenalin is one of the quickest and most powerful pressor substances known. It also slows but strengthens the heart-beat. The effect is very transitory; the maximum is maintained for only a few seconds, and after 30 seconds to 2 minutes — according to the dose — the pressure has returned to normal. The pressure effects are more plainly seen when the slowing of the heart, due to vagus action, is prevented by atropin or by cutting the vagi in the neck. The increase of pressure is due primarily to vaso-constriction. This constriction is greatest in the splanchnic domain, next greatest in the systemic vessels. The vessels of the brain and lungs are subject to the constrictor effects of adrenalin in artificial perfusion; but after injection of adrenalin into the general circulation, the increased pressure elsewhere overcomes the cerebral and pulmonary resistance, and the result is an actual increase of blood-flow in these vessels. Adrenalin is therefore not a suitable agent for use in cerebral or pulmonary hemorrhage. The coronary vessels constitute the most marked exception to the rule in case of adrenalin, for they are insusceptible to the constricting action, and according to most authors the effect is vaso-dilatation. The most recent studies of this subject are the following. Barbour has undertaken to establish a relation between the different effects of adrenalin and the anatomical structure of the walls of the different blood-vessels, without fully definite results. Desbouis and Langlois have found that very small doses of adrenalin cause vaso-dilatation in the lungs, but larger doses cause contraction. Ogawa perfused kidneys, intestinal loops, and musculo-cutaneous vessels with l- and d-adrenalin. With very weak solutions he found sometimes a primary dilatation. Beyond a certain threshold, the effect of adrenalin in all vessels is contraction, which increases with the dosage.

The effects of adrenalin are of purely local origin. Central stimulation is demonstrable in some cases, *e.g.*, when adrenalin

is injected into a carotid artery (Biedl), but this stimulation is probably a secondary result of anemia of the centres. The local constrictor action of adrenalin has made it of use especially as an addition to solutions for local anæsthesia, since it both diminishes hemorrhage and delays absorption of the anæsthetic, thus prolonging the influence of the latter.

Either by vaso-constriction or by modification of the permeability, adrenalin acts powerfully in retarding absorption, not only at the site of its injection, but also throughout the body. Thus Exner (1) discovered that poisoning from intraperitoneal injection of strychnin is greatly delayed when adrenalin is simultaneously injected. Exner (2) proved that a similar delay of absorption occurs when the strychnin is given intrastomachally and the adrenalin, as before, intraperitoneally. Meltzer and Auer likewise witnessed a delay of absorption and excretion of subcutaneously injected fluorescein in consequence of adrenalin injection. Falta and Ivcovic differed with Exner in the interpretation of the phenomena observed, and claimed that adrenalin acts as an antidote to strychnin, and not as a mere constrictor of vessels, delaying absorption. The question was settled in favor of Exner's view by the research of Balint and Molnar, who proved that the power of adrenalin to delay the toxic symptoms of strychnin is abolished by a simultaneous injection of nitroglycerin. But the effect is very marked, and may well be borne in mind by practicing physicians. For example, in Exner's experiments, rabbits which received 5 milligrams of strychnin nitrate intrastomachally died in about 15 minutes; while other rabbits which received the same dose, along with 0.5 cc. adrenalin chloride solution intraperitoneally, survived for 4 to 8 hours. Out of three rabbits poisoned with physostigmin, two died promptly; one recovered. Of three rabbits receiving adrenalin simultaneously with the physostigmin, all recovered. Exner suggested the practical importance of his findings. Bayer (p. 82) quotes writers who recommend adrenalin for snake-bite, and who have found guinea-pigs thus protected against a lethal dose of cobra venom. Theoretically the method should be of therapeutic value in a variety of poisonings, and no reason is apparent why it has not come into more general use.

Josué in 1903 discovered that repeated intravenous injections of adrenalin produce atheromatous changes in the arteries, especially the aorta. The possibility that human arteriosclerosis might

be explained as of adrenal origin promptly gave rise to a large number of investigations. The media is primarily and principally affected; the muscle-fibres degenerate, and fibrous and calcified plaques result. It is reasonably well established that alterations of blood-pressure are not the cause of these changes, but that a direct toxic action of adrenalin is concerned. The subject is illuminated somewhat by the fact that atheromatous changes are rather easy to produce in the rabbit's aorta. Bayer (2) and O. Loeb cite authors who have observed such changes from phloridzin, barium chloride, ethyl-amyl alcohol mixture, digitalin and digalen, strophanthin, adonitin, hydrastin and hydrastidin, mercurial salts, hydrochloric, phosphoric, and lactic acids, calcium phosphate, potassium bichromate, trypsin, pepsin, thyroidin, dessicated mammary gland, and large doses of physiological salt solution. Loeb's study is the most recent; he attributes many of the above results to infections; he finds specific arterionecrosis produced by aliphatic aldehydes, but not by aromatic aldehydes, alcohols, and other substances. While in human patients with arteriosclerosis the adrenalin-content of the blood has been described as increased in some cases, in other typical cases such increase is entirely absent. The arterial lesions produced by adrenalin are not identical with the changes found in human arteriosclerosis. Excess of adrenalin therefore cannot be assumed as the cause of clinical arteriosclerosis. Occasional vascular lesions at human autopsies (*e.g.*, in neuroses and in infections) have been claimed to resemble those produced experimentally by adrenalin. A still smaller number apparently represent the identical thing, for they were found in patients who had received prolonged therapeutic treatment with adrenalin.

Adrenalin has a marked influence upon the lymphatics, probably altogether in the direction of diminishing the flow. Camus reported an increase of lymph-flow, but Tomascewski and Wilenko found the opposite, viz., a diminution and even cessation of the stream. The latter result is more probable, in view of the delayed absorption known to result from adrenalin. Bayer (p. 82) cites authors who have found lymphatic vessels and also stomata contracted by adrenalin in manner analogous to the contraction of blood-vessels.

It is thus seen that the smooth muscular fibres of blood- and lymph-vessels, except of the coronary vessels, are caused to contract by adrenalin. But this effect is not the same for smooth muscle

in all locations. Adrenalin causes *relaxation* of the unstriped muscle of the entire digestive tract; the sphincters (pylorus, etc.) alone constitute an exception, for their tone is increased. Opposite effects are obtainable by sufficiently high dilution (Hoskins). The fibres of the urinary bladder are relaxed. The uterine musculature on the contrary contracts under the influence of adrenalin. This action can be used not only as a test, but also for checking uterine hemorrhage. The effect of adrenalin upon the smooth muscle of the eye has acquired importance as a test. Large doses injected intravenously cause mydriasis in living animals, and the reaction is made more marked by section of the sympathetic or extirpation of the superior cervical ganglion. The reaction is still present in the enucleated eye; frogs' eyes have been the ones commonly employed.

Upon voluntary muscle the effect of adrenalin is less prominent, but is still demonstrable. Isolated muscles treated with adrenalin are poisoned in a manner resembling the effects of fatigue, as judged by the curve of single contractions. But the most important influence of adrenalin upon voluntary muscle is its reviving effect after exhaustion. The return of power to the wearied muscle is more difficult to demonstrate in warm-blooded animals, but appears very plainly in preparations of isolated muscles of cold-blooded species. The reviving influence far outlasts the effects of adrenalin upon the blood-pressure.

Upon the glands, the action of adrenalin is also varied. The salivary glands respond with an increase of secretion of 2 to 9 minutes duration; the saliva produced is of the "sympathetic" type. The secretion of acid in the stomach is said to be increased. The effects of adrenalin upon the pancreas will be considered in Chapter XIX. The liver yields an increased flow of bile under the influence of adrenalin. The effect upon the skin seems to vary with the species; marked sweating in the guinea-pig, and increased secretion of skin glands in the frog have been reported; but no such increase was observed in the cat, and Elliot witnessed decreased instead of increased perspiration in the palm of his own hand when adrenalin was injected under the skin. The effect of adrenalin upon the renal activity will be discussed later in this chapter. The discharge of chromaffin substance from the adrenals is said to be increased by adrenalin injection, so that the brown stain of the cells becomes paler. The pigment cells of animals, such as frogs, contract under the influence of adrenalin.

The cells of nervous ganglia are said sometimes to show changes indicative of exhaustion, but there is no evidence that the action of adrenalin upon them is direct; just as there is no evidence that adrenalin stimulation of the higher nervous centers is due to anything but anemia. Spermatozoa and ova are poisoned by adrenalin. Leukocytes also are poisoned *in vitro* even by high dilutions of adrenalin, but dissolution of erythrocytes is absent. Injected into the living body, adrenalin is said to cause increase of red corpuscles during the first 5 hours, followed by a diminution lasting 2 to 5 days; the number may fall 300,000 to 1,500,000 below normal. Phagocytosis of erythrocytes has been witnessed in animals dead from large doses. Adrenalin injection causes leukocytosis, with various changes in the differential count, including diminution of eosinophile cells. Coagulability of the blood is said to be increased, alkalinity diminished.

5. Properties and Tests of Adrenalin.

The active principle of suprarenal extract was first isolated by Abel in the form of its benzoyl compound, and was called by him epinephrin. Later the crystalline substance was obtained by Takamine and by Aldrich, and the former gave it the name adrenalin, which it generally bears. The most commonly accepted empirical formula is that of Aldrich, $C_9H_{13}NO_3$. It contains a benzol nucleus, and its structure is indicated by the names methylamino-ethanolpyrocatechin or orthodioxyphenylethanolmethylamin. The knowledge of its structure permitted its artificial synthesis, and the synthetic as well as the animal product is now on the market. "Natural" adrenalin is levorotatory. The synthetic substance is racemic. The latter has, however, been split into its d- and l- components. Interesting relations exist between these. The synthetic levorotatory adrenalin is in all respects identical with the product of the chromaffin tissue. The d-adrenalin resembles the other form in physiological action, except that it is far feebler. Racemic adrenalin shows an activity corresponding to its composition of equal parts of the d- and l-forms. Abderhalden and Slavu discovered that mice, which are highly susceptible to poisoning with "natural" adrenalin, can by preliminary treatment with d-adrenalin be protected against several times the lethal dose. Fröhlich found that injections of d-adrenalin produce in animals a condition of resistance, such that even milligram-doses of l-adrenalin have no effect upon the blood-

pressure. Fröhlich explains his own, and also Abderhalden and Slavu's findings, on the assumption that d-adrenalin satisfies and binds the same affinities of the cell as the l-adrenalin, so that the latter can no longer be anchored. Ogawa likewise has found in perfusion experiments that the contracting effect of d-adrenalin is less than that of l-adrenalin; but the secondary dilatation after the former is very difficult to overcome by means of the latter.

Various substances chemically similar to adrenalin have been prepared, and they show to some extent an imitation of its physiological action. Hypotheses have been attempted concerning the mother substance of adrenalin in the body, and tyrosin has been suggested as a source, but nothing is proved. Because of the pigmentation in Addison's disease, the relations between adrenalin and pigments have been investigated. By means of certain enzymes, adrenalin has been transformed into a dark pigment.

The tests of adrenalin are (A) chemical and (B) biological. The fullest review and discussion is by Borberg.

A. Chemical Tests.

Without attempting to mention all the reactions that have been described, a short list of the more delicate and useful ones may be given.

I. Green color with ferric chloride. This test is chronologically first, for it is Vulpian's original discovery. The Pharmacopeia still recommends it for testing adrenal extracts. For finer work, however, especially quantitative, it is neither very delicate nor very reliable.

II. Yellow to reddish-brown color with chrome-salts, the shade varying with concentration of adrenalin. Similar criticisms as for the first test apply. But for demonstrating adrenalin in the tissues, this method still holds a standard position.

III. Red color with iodin solution. The test itself is open to the same criticisms as above. For modifications and their value see Bayer (p. 38).

IV. Red color with mercuric chloride. The liquid supposed to contain adrenalin is treated with a few drops of 1–2 per cent sublimate solution; the red color appears in 1 to 3 minutes and lasts for several hours. It is a little more sensitive than the ferric chloride test.

V. Red color with potassium ferricyanide. The suspected solution is treated with HCl to precipitate albumin, then made

alkaline with ammonia, and a few drops of a concentrated potassium ferricyanide solution added. The resulting red color lasts several hours. Pyrocatechin does not give this reaction.

VI. Reduction of manganese superoxide to colorless lower oxides, with simultaneous oxidation of the adrenalin to the red oxy-adrenalin. The depth of color is proportional to the concentration of adrenalin, and is claimed to be quantitatively reliable in dilution as low as 1 : 1,000,000. The color lasts several hours.

The red color mentioned in most of the above tests is likewise due to oxy-adrenalin, which is the same substance as causes solutions of adrenalin to turn red on standing.

B. Biological Tests.

The biological are more delicate than the chemical tests. Those most commonly used are the following.

I. Intravenous injection, preferably in vagotomized animals. A very few cubic centimeters of blood from the adrenal vein, for example, will suffice to produce a well-marked increase of blood-pressure in an animal whose vagi have been cut.

II. Mydriasis of the enucleated frog's-eye. Meltzer studied this mydriasis in living animals, observed the same reaction in the enucleated eye, and suggested it as a test. Ehrmann worked out all the details of the test, and its general adoption dates from his work. It is said to react positively to adrenalin in 1 to 20 million dilution. Hoskins considers the test ordinarily reliable only for 1 to 5 million dilution, but by special methods obtains positive results in 1 to 100 million dilution. He mentions the recognized disadvantages of this test, viz., lack of sharpness and insufficient delicacy, but points out its one special advantage, viz., its suitability for use with very small quantities of solution.

III. Meyer's method of isolated segments of blood-vessels. A graphically demonstrable contraction is said to be produced by adrenalin in dilution of 1 to 1000 million. This is one of the best and most delicate tests.

IV. The Laewen-Trendelenburg method of measuring the rate of flow of Ringer solution in artificial perfusion of the hind-quarters of frogs. Adrenalin in 1 to 5 million dilution is said to diminish the flow by 87–96 per cent. In 1 to 50 million dilution, the outflow of liquid is claimed to be reduced by 50–81 per cent. A change from adrenalin to an indifferent solution restores the

former rate of flow. In this test, and also with that of Meyer, it is necessary to provide suitable controls against the constricting action of foreign serum itself, in view of the observations of W. H. Schultz. The perfusion method has been considerably used because of its convenience along with its considerable delicacy.

V. The uterus-strip method of Fraenkel and Allers. This has been one of the favorite tests. Ott and Scott (2) proved that the contraction produced by adrenalin is imitated by a number of different organ-extracts; it is therefore not a specific test. Hoskins found the test an advantageous one for dilutions of 1 to 20 or 30 million, but subject to error in higher dilutions.

VI. The relaxing effect of adrenalin upon isolated strips of intestine (Magnus. Cannon and de la Paz). The animal furnishing the strip must be killed by a blow or anæsthetized with urethane; ordinary anæsthetics interfere with the reaction. Hoskins finds the reaction demonstrable in dilution of 1 to 100 million, and gives this method the highest position of all on the basis of convenience, delicacy, sharpness, and specificity.

Recent investigations have contributed greatly to the difficult question of adrenalin tests. The principal problem has been to exclude false reactions, due to substances which imitate adrenalin. O'Connor made a comparative study, using the Fraenkel uterus-strip and the Laewen-Trendelenburg perfusion method. He found that adrenalin-like substances are produced in the clotting of blood, so that only plasma and not serum should be used for tests. Adrenalin can be demonstrated in the adrenal-vein blood by the above tests, but not in the peripheral blood when plasma is used. He considers it not possible at the present time to form any accurate idea of the normal concentration of adrenalin in the blood. Kahn (5), on the other hand, still considers the serum suitable for use.

The combined methods lately introduced by American authors represent the highest development of the technique, and will doubtless win exclusive use. Many sorts of stimulation cause contraction of smooth muscle, but not many stimuli except adrenalin produce both contraction of certain structures and relaxation of others. Stewart has combined on this basis the uterus-strip and the intestine methods. He finds that adrenalin cannot be detected in the peripheral blood. Using hirudin to prevent clotting, he found absolutely identical effects produced by serum and plasma. O'Connor's work was with homologous blood, where-

as Stewart used heterologous blood, as necessary for clinical purposes.

Janeway and Park combined the use of carotid or mesenteric artery (ox), which is constricted, and coronary artery, which is relaxed. They confirmed O'Connor. Working with defibrinated blood or serum, a vaso-constrictor substance was found, but it obviously was not adrenalin, for it contracted the coronary the same as the peripheral vessel. Working with whole blood, they found no effect upon either carotid or coronary, but prompt contraction when the same blood was defibrinated. This constrictor substance is not "adrenalin-like," but rather like barium chloride, for it acts directly on the muscle, not on the sympathetic.

6. Point of Attack of Adrenalin.

The seemingly bizarre and irregular effects of adrenalin — now contraction, now relaxation of muscle-fibres, etc. — are explained by a knowledge of its mechanism and point of attack. For a clear view of this subject, an understanding of certain present-day doctrines concerning the nervous system is essential. The question involves especially the distinction between *sympathetic* and *autonomic* nerves, and is clearly and briefly elucidated by Biedl (3). The following is an abstract of his account.

The classical division of the nervous system is into (1) cerebrospinal or animal, and (2) sympathetic or vegetative. The two are connected through the *rami communicantes*. An essential difference however consists in the fact that in the first system, *one* neurone extends all the way from the brain or cord to the periphery, while in the second system, at least one ganglion-cell is intercalated in this path. Therefore in the first system the impulse is direct; but in the second system it is indirect, by relay, and opportunity for important modifications of the impulse by the ganglion-cells is afforded.

The nerves for the control of the voluntary muscles leave the spinal cord by an unbroken series of anterior root fibres. But the efferent nerves for the supply of unstriped muscle and other involuntary structures pass out in three divisions, separated by the roots of the brachial and lumbar plexuses. These three divisions are (1) the cranio-cervical, above the brachial plexus; (2) the thoracico-lumbar, between the brachial and lumbar plexuses; (3) the sacral, below the lumbar plexus. English writers (Gaskell, Langley) established this division, and intro-

duced the term *autonomic* to cover the entire system, comprising all nerves to involuntary organs. According to them, the *sympathetic* system, in a narrower sense, included only the second of the above divisions, viz., the nerves springing from the gangliated cord of the sympathetic in the thoracic and abdominal cavities. Later writers, especially German, have followed this definition of the term *sympathetic;* whereas all the rest of the vegetative system has been grouped by them under the name *autonomic.* The idea may become clearer in tabular form.

Vegetative nervous system.	A. Sympathetic.....	Consists of all nerves springing from the gangliated cord in the thoracic and abdominal cavities.
	B. Autonomic.....	Consists of two portions: 1. Cranio-bulbar, viz., the fibres from the mid-brain and medulla distributed through the oculomotor, facial, glossopharyngeal, and vagus nerves. 2. Sacral, viz., the fibres from the lower lumbar and sacral cord, distributed through the pelvic nerve.

The sympathetic and autonomic systems are thus viewed as distinct and even opposed. The sweat-glands and pilomotor muscles of the skin, also the blood-vessels of certain viscera, receive an exclusively sympathetic supply. All other smooth muscle of blood-vessels and viscera, and all the glands, receive innervation from both the sympathetic and autonomic systems. In some cases the nerves from these two sources are actually antagonistic, but very frequently the antagonism is not between systems, but between nerves of the same system, *i.e.*, augmentor and inhibitory fibres from the sympathetic, and augmentor and inhibitory fibres from the autonomic system, for the same organs.

The difference upon which the distinction between sympathetic and autonomic systems essentially rests is chemical. Differences in the chemical nature of the nerve-endings are indicated by the selective action of certain poisons. Langley and Dickinson showed that nicotin first stimulates and then paralyzes ganglia where the relay of nervous impulse occurs. Either intravenous injection or local application suffices for this effect, which applies to the entire vegetative system. Unless the cells of a given

ganglion constitute a relay-station for a given nervous tract, painting the ganglion with nicotin has no effect upon nerve-impulses passing along this tract. If the ganglion in question does constitute such a relay-station, painting with nicotin blocks nerve-impulses by paralyzing the preganglionic fibres, while the postganglionic fibres are able to respond to stimulation in the usual way. The effect of other poisons upon the activities of the sympathetic and autonomic systems, and the chemical differentiation thus indicated, are given in a detailed table by Biedl. The briefer table of Fröhlich and Loewi will convey the general idea.

	Augmentor.		Inhibitory.	
	Stimulation.	Paralysis.	Stimulation	Paralysis.
Autonomic	Pilocarpin	Atropin		Nitrites
Sympathetic	Adrenalin	Ergotoxin	Adrenalin	

Pilocarpin may here be taken as representative of the "muscarin group," comprising muscarin, pilocarpin, and physostigmin.

Adrenalin is here seen to take its place with other drugs acting specifically upon certain nerves. Furthermore, its effect is seen in each case to be a stimulation of the sympathetic system. The apparently irregular action of adrenalin upon various structures is thus explained; for its effect is always the same as that produced by stimulation of the sympathetic nerves passing to the organ in question. Where the sympathetic impulse causes contraction, as in the blood-vessels and the uterus, adrenalin likewise causes contraction. Where the sympathetic impulse causes relaxation, as in the intestine, adrenalin likewise causes relaxation. In other words, adrenalin excites the sympathetic function, whether this function be augmentation or inhibition.

The point of attack of adrenalin is, however, not any part of the sympathetic neurone itself. After section and complete degeneration of the sympathetic nerves passing to a given structure, adrenalin exhibits its usual effect, even in increased degree. On the other hand, adrenalin does not act directly upon the muscle-fibres, because (1), according to the embryological studies of Scott-Macfie, muscle which has not yet received a nerve-supply is

insusceptible to adrenalin, and (2) Brodie and Dixon found that after paralysis of nerve-terminals by apocodein, the muscle-fibres fail to respond to adrenalin, though a known direct stimulant of the muscle, such as barium chloride, still produces its usual effects. The conclusion was therefore reached that the structure stimulated by adrenalin is something intermediate between the nerve and the muscle. The terminal network of the nerve fibrils might be such a structure, but it was ruled out by experiments of Elliott, showing especially that the effect of adrenalin is independent of integrity or degeneration of these networks. Accordingly, it is now believed that adrenalin acts upon the *myoneural junction*, a structure not histologically demonstrable, intermediate between nerve and muscle, but dependent upon the muscle-cell for its nutrition. As the contractile substance is specialized for contraction, so also the substance of the myoneural junction ("receptive substance" of Langley) is specialized for receiving stimuli. Its composition is supposed to determine the nature of response of the muscle to a stimulus, *e.g.*, whether it responds by contraction or relaxation. If a muscle has no sympathetic innervation, it lacks this myoneural junction, and accordingly cannot respond to adrenalin.

The distinction between sympathetic and autonomic systems has received clinical application chiefly in Germany. A few points of interest have developed, such as Loewi's adrenalin-mydriasis. In general, however, no clinical importance has yet been established for this distinction. The solid methods of the English physiologists have not been emulated, and most of what has been written concerning "sympathetic" and "autonomic" in recent clinical literature is pure fancy.

7. Dosage and Effects of Adrenalin.

The typical effects of adrenalin are produced by intravenous injection. The fatal dose by this method has been found by various authors [see Bayer, p. 127] to be 0.1–0.2 mg. per kilo for guinea-pigs and rabbits, 0.1–0.25 mg. per kilo for dogs, and 0.5–0.8 mg. per kilo for cats. The high resistance of cats corresponds to the larger doses required for ordinary physiological effects in them. The threshold dose for perceptible effects upon the blood-pressure is stated to be 0.0003 mg. per kilo in rabbits, and 0.012 mg. per kilo in cats. White mice are exceedingly susceptible to adrenalin. Individual animals sometimes show far higher or

lower resistance than the average of their species. The symptoms leading to death are generally dyspnea, convulsions, and weakness. In rabbits there is often a rapidly fatal œdema of the lungs. Autopsy may show pulmonary hyperemia and œdema, effusions of fluid in serous cavities, parenchymatous hemorrhages in thymus, adrenals, anterior lobe of hypophysis, and liver; cloudy swelling of kidneys or parenchymatous nephritis.

The brief duration of the effects of intravenously injected adrenalin has previously been mentioned. At first, authors supposed that adrenalin must be quickly excreted or destroyed. In frog experiments, Weiss and Harris were able to prove the contrary. By tying off one of a frog's hind-legs, and injecting adrenalin into the general circulation, they were able to follow the characteristic contraction of vessels in the web of the free foot. After these effects had passed off, they untied the ligature of the other leg, and saw the contraction now appear in its web. De Vos and Kochmann found that increased adrenalin concentration of the blood can be demonstrated 10 minutes after the injection, *i.e.*, when the pressor effects have entirely passed away. Ehrmann (1*A*) proved in cats that adrenalin injected into the blood disappears not rapidly but slowly, and furthermore that adrenalin in the concentration ordinarily effective is still present in the blood at a time when all effects have passed away. The presence of adrenalin after disappearance of the pressor effects was also proved by Kahn (4). Weiss and Harris believed the transitory action to be due to weariness of the vasomotor mechanism. But Kretschmer proved that each of a series of rapidly repeated adrenalin injections produces the same effect as the first. The phenomenon was thus brought into line with Straub's law of the action of certain alkaloids, viz., that these substances act not when outside a cell nor after arriving inside a cell, but solely during the process of entering into the cell. Not the absolute concentration, but the relative concentration inside and outside the cell, is thus the determining factor. A prolonged adrenalin action can be maintained by continuous intravenous infusion of a very dilute adrenalin solution. According to Falta and Ivcovic, adrenalin undergoes a change shortly after injection; only after long standing of the serum on ice does the free adrenalin reappear. There may perhaps be confusion here with adrenalin-like substances. All the above statements signify only the relatively slow disappearance of considerable doses of adrenalin from the blood; the

substance is present after the effects are gone. It still remains a fact that adrenalin is quickly destroyed in the blood and tissues. O'Connor has found evidence that the normal trifle of adrenalin reaching the tissues through the blood is rapidly consumed by them.

Adrenalin is unable to penetrate the intact skin or mucous membranes. Doses by mouth are practically without effect, though adrenalinuria has been claimed after very large intra-stomachal doses. Adrenalin is highly resistant to digestion and to bacteria. Falta and Ivcovic (1) advanced the hypothesis that adrenalin is bound by the mucous membrane in some inactive form, and that this compound is later broken up and destroyed in the liver.

Subcutaneous injection of adrenalin produces glycosuria but practically no circulatory effects in laboratory animals. In human patients, on the contrary, the blood-pressure can be raised by subcutaneous injections; *e.g.*, a dose of 0.5 mg. subcutaneously is said to produce a rise of blood-pressure within 5–12 minutes, which remains at its maximum for 2–3 hours. Locally, adrenalin tends to cause necrosis. With small doses the effect may not be noticed, but in giving the usual glycosuric injections in laboratory animals, ulceration is common. Small amounts of strong solution are preferable from this standpoint, for dilution merely renders ulceration more certain and more extensive. The constitutional effects of sloughing areas may not be altogether negligible in metabolism experiments. The fatal dose subcutaneously in guinea-pigs and rabbits is said to be 8–10 mg. per kilo, in dogs 5–6 mg. per kilo. The symptoms are vomiting, diarrhea, and prostration. Ordinary doses in human patients are sometimes followed by headache, palpitation, and even chills. Aschner has noted that this reaction is extreme in Basedowoid patients.

The glycosuric effects are prompter and more intense after intraperitoneal than after subcutaneous injection of adrenalin. The lethal dose is about the same. Though superficial ulcerations are thus avoided, the method is said to be on the whole somewhat more dangerous than subcutaneous administration.

By any mode of administration, the excretion of adrenalin is very slight. A trifle is claimed to appear sometimes in the urine, but the presence of substances which imitate or modify the adrenalin reactions makes the tests uncertain.

8. Influence of Adrenalin Upon Metabolism.

This subject may be considered under four headings, according to the influence exerted upon the economy of:

A. Inorganic substances.
B. Fat.
C. Protein.
D. Carbohydrate.

A. Inorganic Substances.

Oliver and Schaeffer found that intravenous injection of adrenalin results in a prompt cessation of urine. Bardier and Frenkel determined that the intravenous injection of a small dose of adrenalin causes, along with the general increase of blood-pressure, a specially marked vaso-constriction in the kidney, accompanied by oliguria or anuria. After 2 or 3 minutes, the renal vessels dilate and polyuria sets in, and may continue as long as 9 minutes. Since the dilatation and diuresis are of such comparatively long duration, the authors think they are not merely secondary to the vaso-constriction. Schlayer occasionally observed increase of diuresis when an intravenous injection of adrenalin had been preceded by an intravenous saline infusion. Pollak (1) found the diminution of urine after intravenous adrenalin injection so marked that it constituted an obstacle to glycosuria; only by diuretin or large saline injections could diuresis be kept up. With subcutaneous injection of adrenalin, on the contrary, Biberfeld (2) observed diuresis in rabbits, and the findings of Schatiloff were similar. Slight polyuria has been observed under similar conditions in human patients. Biberfeld also found that the chloride concentration of the urine is diminished by adrenalin injected subcutaneously. Generally diuresis is present to such degree that the absolute excretion of chlorides is increased. If, however, diuresis is absent, the chloride output is diminished. Schatiloff worked out a similar rule concerning other salts, especially phosphates. Falta (5*A*) and co-workers found that adrenalin may increase the phosphorus-excretion to three times, the potassium and sodium excretion to four times the normal; the entire change is in the urine; the salts of the feces are unchanged. On the other hand, Quest asserts that the total calcium excretion is increased by adrenalin, but that most of the increase

is through the feces, while the quantity in the urine is actually diminished.

Adrenalin has been drawn into relation with most human ailments, and among these are the chronic disorders of mineral metabolism represented in rickets and osteomalacia. Stoeltzner founded the idea, by a series of observations upon the adrenals of children dead after rickets and other diseases. By comparisons of the weight and the adrenalin content, he concluded that there is a deficiency of adrenalin in rickets. In guinea-pigs and rats, removal of one adrenal was claimed to produce, in a few of the animals, disorders of locomotion and abnormal formation of osteoid tissue in the ribs. Stoeltzner claimed to have treated rickets successfully with adrenalin injections. He attributed to it a specific stimulant influence for the transformation of osteoid into finished bone-tissue.

Quest was unable to confirm Stoeltzner's findings. Jovane and Pace agreed that adrenalin injections in rachitic children seemed to improve appetite, nutrition and muscular tone. But they found no abnormalities of the adrenals in rachitic children nor in rabbits with experimental rachitis, nor any appearance of rachitis after removal of one adrenal in young puppies. At least from the standpoint of pathological anatomy, the authors reject any relation between the adrenals and rickets.

Bossi applied Stoeltzner's principles to osteomalacia. He claimed (1) that the disease comes on in sheep within a few days after removal of one adrenal; (2) that adrenalin injections in young puppies and rabbits produce ossification of the bones earlier than in the controls of the same litter; and (3) that adrenalin is of marked therapeutic value in clinical osteomalacia. Concerning the first claim, those who have experience with unilateral epinephrectomy will agree that osteomalacia is not produced in ordinary laboratory animals by this operation. The second claim may be compared with a recent paper by Etienne, in which adrenalin is described as causing *decalcification* of an osteomalacic type. The third claim of Bossi is for clinicians to decide; but it is not justified to attribute to adrenalin a specific action.

B. Fat Metabolism.

Blum (2) asserted that fasting dogs show only rare or slight glycosuria from adrenalin, but that feeding with oil causes the

reaction to appear. Eppinger, Falta and Rudinger claim that fat metabolism is increased in adrenalin glycosuria, and that fat feeding increases the sugar excretion. Ringer disproved these claims by showing that in maximally phloridzinized animals, free from glycogen, injection of adrenalin does not cause any extra elimination of sugar. The high D/N ratio of Eppinger, Falta and Rudinger is explained as due to elimination of carbohydrate already present in the organism. Adrenalin does not cause a conversion of fat into carbohydrate.

C. Protein Metabolism.

Blum found that the nitrogen excretion is not perceptibly modified by adrenalin either in fed or in fasting dogs.

Noel-Paton reported no change in the protein metabolism of well-nourished dogs and rabbits, but an alteration in the distribution of the urinary nitrogen. In insufficiently nourished dogs he observed an increase in the nitrogen excretion.

Underhill and Closson (2) confirmed the last observation, but proved that the distribution of urinary nitrogen is not changed by adrenalin.

Wolownik found no change in protein katabolism from adrenalin in rabbits on fixed diet.

Eppinger, Falta and Rudinger reported a marked increase in the nitrogen excretion of fasting dogs under the influence of adrenalin. An opposite change occured in thyroidectomized dogs.

Quest observed a loss of nitrogen in a full-fed dog during three days of adrenalin treatment, as compared with preceding and following control periods.

Hirsch and Kraus [ref. by Bayer] obtained no increase of nitrogen output from either subcutaneous or intravenous injections of adrenalin.

Schatiloff, in a series of rabbits under identical conditions, saw sometimes an increase of nitrogen excretion and sometimes none.

Bayer (1) found no increase of nitrogen excretion in one fasting rabbit in consequence of subcutaneous injection of adrenalin, but in two fed rabbits the nitrogen was increased and a positive was changed to a negative balance.

Since there are so many negative results, it may be concluded that adrenalin has no direct influence upon protein metabolism.

The positive reports are perhaps explainable by local tissue-necrosis, fever, sweeping out of nitrogen by diuresis, and possibly formation of carbohydrate from protein.

D. Carbohydrate Metabolism.

The influence of adrenalin injections upon carbohydrate metabolism may be discussed under the heads of:

(I) Adrenalin glycosuria.

(II) Its modification by various conditions.

(III) Its mechanism and relation to other forms of glycosuria.

I. Adrenalin Glycosuria.

Blum in 1901 announced the discovery that adrenal extract injected subcutaneously gives rise to glycosuria. Positive results from intravenous injections were also reported, but mouth-feeding was found negative. His second paper (2) was devoted to extension of the original work, and production of glycosuria by means of the active principle, adrenalin.

Metzger proved definitely that the glycosuria results from hyperglycemia. Numerous later workers have verified the fact. Bierry and Gatin-Gruzewska, Noel-Paton, Wolownik and others have demonstrated the marked loss of liver-glycogen from large doses of adrenalin.

Adrenalin glycosuria can be produced in all common laboratory animals, including the frog (Velich). It has also been reported in man [von Noorden, Garrod (3)].

The dose required is small (0.01–0.1 mg. adrenalin). Glycosuria begins in ½–2 hours, and lasts generally in the neighborhood of 3 hours, though Blum has reported instances in which it persisted 2 or 3 days. The percentage of dextrose in the urine may be low or very high. The presence of sugar, and especially the absolute quantity excreted, is governed in large measure by diuresis.

La Franca found that in adrenalin glycosuria in dogs, the quantity of absorbed O_2 and of excreted CO_2 are both increased, while the respiratory quotient is unchanged.

Hari, using dogs, found that adrenalin in doses of 0.5–1 mg. per kilo intraperitoneally, or 0.1–0.2 mg. per kilo intravenously, produces demonstrable changes in the respiratory quotient. In curarized animals, there is a diminution of O_2-consumption and

a smaller diminution of CO_2 output. The quotient is thus raised, and an increased burning of carbohydrate is indicated.

Fuchs and Roth, in human patients, found that adrenalin increases both O_2 consumption and CO_2 excretion, and raises the respiratory quotient. An increased combustion of sugar is indicated. The mechanism is not decided; the authors think it might be a simple effect of hyperglycemia, or some action of adrenalin as a catalyzer of a sugar-splitting ferment.

Wilenko (4), using rabbits under urethane, found adrenalin to produce little or no change in the respiratory quotient.

II. Modification by Various Conditions.

(*a*) *The Glycogen Supply.*

Blum at first supposed that adrenalin glycosuria occurs in animals starved entirely glycogen-free; but later he found it necessary to reverse this opinion. Herter and Richards proved that prolonged fasting with phloridzin poisoning reduces dogs to a condition in which adrenalin gives rise to no glycosuria. Noel-Paton has argued for a sugar-formation from albumin, and Eppinger, Falta and Rudinger upheld the same view. The latter found that depancreatized dogs, supposed to be practically glycogen-free, showed increase of sugar-formation under the influence of adrenalin. Ringer considered the animals to be not glycogen-free. He therefore made normal dogs glycogen-free by a combination of hunger, cold and phloridzin, and found then that adrenalin produced no glycosuria.

Wilenko (4) still interprets the experiments with depancreatized dogs to mean that adrenalin glycosuria is not dependent upon a supply of glycogen.

The evidence would seem capable of interpretation as follows.

(1) Adrenalin may under suitable conditions cause formation of glycogen from protein. Pollak (1) made rabbits glycogen-free by starvation and strychnin, and then by small increasing doses of adrenalin was able to bring about a formation of new glycogen. The quantities which these fasting animals thus stored in their livers attained values only equalled in animals fed on carbohydrate.

(2) Adrenalin does not produce glycosuria in normal animals which have been made glycogen-free.

(3) Adrenalin will probably produce glycosuria in glycogen-free diabetic animals, or will cause an excretion of sugar in excess of the quantity of glycogen present. Animals nearly or totally depancreatized are much more prone to most forms of glycosuria than normal animals, for reasons stated hypothetically in Chapter VII. It has been demonstrated that piqûre will produce glycosuria in these animals when they are so far gone that spontaneous glycosuria has ceased, and when a non-diabetic animal would certainly show no glycosuria. It is probable that the action of adrenalin will be found similar.

(*b*) *Repetition of Dose.*

Underhill and Closson (2), also Underhill (4), have noted the fact that the same dose of adrenalin at different times in the same animal may cause a very different degree of glycosuria. Various authors had previously determined that prolonged treatment with adrenalin does not cause a continuance of the same glycosuria (as with phloridzin), nor an increase of glycosuria (as would be the case if the condition were diabetic); but, on the contrary, the animals soon attain a condition in which adrenalin no longer produces glycosuria. Pollak (1) studied the question most fully, and found that the repeated injections continue to cause hyperglycemia, but for some unknown reason the permeability of the kidney is altered, so that sugar fails to pass into the urine. Other authors have found a corresponding increase of resistance of treated animals to the other toxic effects of adrenalin [see Bayer (2), p. 130]. Such animals may acquire a high tolerance. There is no true immunity to adrenalin. The blood of resistant animals has no power to protect other animals, and all attempts to demonstrate an "anti-adrenalin" have failed. The cause of the increased tolerance is unknown.

(*c*) *Phloridzin.*

Mention has already been made of Ringer's proof that at the height of phloridzin glycosuria, adrenalin causes no increase of sugar excretion.

In animals not maximally phloridzinized, Erlandsen (2) found that adrenalin glycosuria is superposed upon phloridzin glycosuria, and the sugar excretion from the two together is greater than the sum of the excretion from the two separately.

(*d*) *Levulose.*

Pollak (1) fed glucose or levulose to rabbits after 4-day fasts, and then injected adrenalin. He admits that the method is an uncertain one, but believes the conclusion justified that the glycogen formed from each sugar is equally resistant to large doses of adrenalin, but to small doses, the glycogen after levulose feeding is more resistant.

Porges (1 and 3) found that within a few hours after removal of both adrenals, the glycogen of dogs' livers becomes reduced to traces, though there may have been weeks of preliminary overfeeding with starch and sugar. In later experiments [ref. by von Noorden (1), p. 50] he found that moderate quantities of glycogen persist in the liver, if the preliminary feeding has been with levulose instead of dextrose.

Zuelzer (1) drew the conclusion that the liver is the point of attack in adrenalin glycosuria, because after adrenalin injection, the feeding of as little as 5 g. levulose to a cat resulted in levulosuria. Wolownik on the contrary observed that adrenalin still causes glycosuria, not levulosuria, after levulose feeding. The conflict with Zuelzer's results is only apparent, not real; for Wolownik used adrenalin after the levulose had become stored as glycogen.

Reichenstein (2) found that small doses of adrenalin increase the tendency to alimentary glycosuria in human patients, and that the tendency to excrete dextrose is increased more than the tendency to excrete levulose.

(*e*) *Various Drugs.*

Starkenstein (1) found that adrenalin glycosuria is not prevented by glycerin. The fact is worth noting, as presenting one distinct difference between adrenalin glycosuria and piqûre glycosuria.

Underhill (4) observed that urethane increases the glycosuric effect of adrenalin. Intravenous injection of adrenalin in very dilute solution fails to produce glycosuria in normal rabbits, but produces it in rabbits narcotized with urethane.

Starkenstein (3) came to the conclusion that anæsthetics have an effect upon the same nerve-terminals as adrenalin. Two stages are distinguishable, in tests with chloral hydrate and paraldehyde. First, there is a stage of increased excitability, in which the anæsthetic increases the glycosuric effect of adrenalin. Light

narcosis with magnesium sulphate has a similar influence. Second, with deep narcosis, there is a stage of diminished excitability, in which the glycosuria from adrenalin or piqûre is diminished or absent. Sugar-puncture performed in deep anæsthesia still produces the usual histologic picture of adrenal exhaustion, and only the benumbing of the terminals is the reason for the absence of glycosuria. Starkenstein also found that antipyretics — antipyrin, quinine, sodium salicylate and sodium benzoate — may have some effect in diminishing adrenalin glycosuria. This effect is distinguished from that of a substance such as sodium tartrate; the latter merely interferes with elimination of sugar by altering renal permeability, whereas the antipyretics oppose the nervous action of adrenalin. Sodium phthalate and sodium bicarbonate are without effect.

Caffein and other diuretics are known to increase the sugar-excretion in most forms of glycosuria. Drugs of the caffein group are themselves causes of glycosuria, by central stimulation. A summation of glycosuric effects of caffein and adrenalin is therefore to be expected, and was demonstrated with suitable doses by Starkenstein. But with too large a dose of caffein, adrenalin glycosuria is found to be actually diminished. The author attributes this effect to a paralysis of the special nervous mechanism. Since the rabbit died the same day, general weakness may also be considered a factor.

Cocain is known to reënforce the other effects of adrenalin, and Starkenstein proved that it also increases adrenalin glycosuria.

Kepinow has found that hypophyseal extract increases the vasomotor effects of adrenalin by sensitizing the point of attack. The increase of adrenalin glycosuria by hypophyseal extract, observed by Falta, is perhaps thus explainable.

Adrenalin glycosuria is diminished or prevented by injection of any one of a long series of substances which have nothing in common except that they injure the kidneys either directly or through nervous shock [see Chapter XIX]. Perhaps sodium carbonate (Frugoni) belongs in this list. At any rate, it comprises pancreatic extract and juice, lymph, spermin, normal serum, Witte peptone, hirudin, crab-muscle extract and all lymphagogues, aleuronat, turpentine, and specific renal poisons, particularly the salts of glutaric, tartaric and some related acids. These substances do not modify the pressor effects of adrenalin. Calcium chloride (Schrank) prevents adrenalin glycosuria; probably the

main reason is the nervous depression; it antagonizes also the effect of adrenalin on the frog's eye.

Miculicich has found that hirudin injected intravenously not only prevents adrenalin glycosuria, but also diminishes the hyperglycemia. Part of its action is a modification of the diuresis, though the NaCl excretion is not inhibited. Ergotoxin injected intravenously or subcutaneously before adrenalin diminishes or prevents glycosuria, according to the dose; when given later, it cuts short a glycosuria already begun. Diuresis is somewhat diminished, but not the NaCl excretion. The effect upon the glycosuria is due to diminution of the hyperglycemia and of the renal permeability.

Neubauer (4), studying anti-glycosuric agents, especially anæsthetics, found that piqûre-glycosuria is inhibited most completely by chloral hydrate, less strongly by alcohol, and least of all by morphin or pantopon. He confirmed the observations of Kahn and Starkenstein that these drugs do not prevent the adrenal exhaustion. Neubauer proved that the inhibitory effect of anæsthetics is only partly upon the kidney; hyperglycemia is also largely prevented. A pairing with glycuronic acid, thus using up the available carbohydrate, is also excluded; and a direct antagonism between adrenalin and the anæsthetic is therefore supposed. This antagonism is believed to consist in the constricting effect of adrenalin and the dilating effect of anæsthetics upon the blood-vessels of the liver. The experiments by which Neubauer supports this view are interesting, but the interpretation must be rejected, for various reasons, including the following; piqûre-glycosuria is not a simple adrenalin glycosuria; it occurs also in epinephrectomized cats; the glycosuria from liver-stasis or asphyxia or pressor substances like barium chloride is insignificant compared to the intense excretion after piqûre; adrenalin produces its pressor effects after intravenous injection with little or no glycosuria, while in the intense glycosuria following subcutaneous injection the pressor effect is absent or minimal. Starkenstein's simple explanation remains the best, viz., that anæsthetics depress the nervous mechanism. This is in accord with the whole series of researches, which show that calcium chloride or thyroidectomy or other agencies which diminish nervous excitability diminish piqûre or adrenalin glycosuria, and parathyroidectomy or drugs which increase nervous excitability increase adrenalin and related forms of glycosuria.

(*f*) *Body-temperature.*

Fever apparently diminishes somewhat, but does not prevent adrenalin glycosuria. Renal disturbances, if they accompany the fever, may be of greater influence than the fever itself. For references to the researches covering this question see Loewi (4), p. 1181.

(*g*) *Operations.*

1. *Thyroidectomy.* — Eppinger, Falta and Rudinger asserted that after thyroidectomy with preservation of the parathyroids, adrenalin produces no glycosuria. Grey and de Sautelle seemed to give partial confirmation, by finding that after thyroidectomy adrenalin glycosuria is greatly reduced, and that with regeneration of the thyroid, or thyroid feeding, the glycosuric action of adrenalin returns. Pick and Pineles also found that in young goats, the diuretic and pressor effects of adrenalin are present after thyroidectomy, but the glycosuria is absent. But in rabbits, they found that thyroidectomy does not prevent adrenalin glycosuria. Underhill and Hilditch then proved the inexactness of the statement of Eppinger, Falta and Rudinger, and the occurrence of adrenalin glycosuria in thyroidectomized animals was further maintained by Underhill (3). Ritzmann showed that the failure of adrenalin glycosuria after thyroidectomy is merely one of the acute toxic or nervous effects following thyroid loss. The diminution of the power of adrenalin runs parallel with the other acute symptoms, and when these have passed away, adrenalin again produces its usual glycosuria. The presence or absence of the thyroid is therefore not a determining factor in adrenalin glycosuria.

2. *Parathyroidectomy.* — After panthyroidectomy, glycosuria and lowered sugar-tolerance were reported by Falkenberg and by Hirsch (2); but Eppinger, Falta and Rudinger proved that only the loss of the parathyroids is responsible for these symptoms. After total thyroidectomy, adrenalin produces more intense glycosuria than in normal animals. Hirsch (3) confirmed the fact that the lowering of tolerance is due to loss of the parathyroids and not of the thyroid. The change occurs only in connection with other symptoms of tetany, therefore does not begin till some five days after operation. Eppinger, Falta and Rudinger proved that partial extirpation of parathyroids is followed by various degrees of lowering of carbohydrate tolerance, even when no symptoms of tetany are visible. It still remains probable that

the effects of total and of partial parathyroidectomy differ in degree rather than in kind, and that the toxic or nervous condition is the essential factor in each case.

3. *Hypophysectomy.* — Aschner found that hypophysectomized dogs react very slightly to adrenalin, and show no glycosuria. The local necrosis at the site of injection was also found not to occur.

4. *Epinephrectomy.* — Schwarz found that epinephrectomized rats, some time after the operation, acquire an extreme sensitiveness to adrenalin. Phloridzin is likewise highly toxic, but yet its toxic effects are greatly delayed by small doses of adrenalin. Other authors, working with other animals (*e.g.*, rabbits) have reported no such conditions following epinephrectomy.

Bierry and Mme. Gatin-Gruzewska observed that in epinephrectomized rabbits, adrenalin generally produces anuria; but in dogs, glycosuria results as usual. Bierry and Malloizel, studying the question in greater detail, found that hypoglycemia is always present in dogs after removal of both adrenals. Injections of adrenalin raise the blood-sugar to its former value, or higher, and may also produce glycosuria; but the doses required are larger, and the hyperglycemic and glycosuric effects are briefer and of less degree than in normal animals. Gautrelet and Thomas (1) found that epinephrectomy prevents adrenalin but not phloridzin glycosuria. Evidently animal species, dosage, operative methods, and length of time after operation are factors in such experiments. It may be concluded that the susceptibility to the glycosuric action of adrenalin is diminished but not abolished by epinephrectomy.

5. *Splanchnicotomy.* — Pollak (2) proved that adrenalin glycosuria occurs after cutting the splanchnic nerves of both sides. Bierry and Morel later reported that in old dogs, intrathoracic section of both splanchnics inhibits adrenalin glycosuria, but in young dogs (one year) splanchnicotomy is without effect upon adrenalin glycosuria. The validity of this distinction must be considered dubious. In general, the fact must be accepted that adrenalin glycosuria is independent of the integrity of the splanchnic nerves.

6. *Exclusion of Liver.* — Velich found that removal of the liver prevents adrenalin glycosuria in frogs. Lepine (3*A*) disabled the hepatic mechanism by section of the spinal cord in the lower cervical or upper dorsal region, and found that adrenalin was then

without glycosuric effect. Falta and Priestley tied the aorta and vena cava just below the diaphragm, so as to exclude the liver, and found that the blood-sugar rapidly fell, and could not be raised by adrenalin injection. Michaud found that adrenalin causes no hyperglycemia in Eck-fistula dogs, and also confirmed the statement of Frank and Isaac (2, 3, 4) that no hyperglycemia results from adrenalin injection in rabbits at the height of phosphorus poisoning.

7. *Venesection.* — Wilenko (5) has found that successive venesections in rabbits diminish adrenalin glycosuria, with undiminished hyperglycemia or diuresis. The effect is due to diminished renal permeability; the hydremia resulting from hemorrhage produces swelling of the epithelium in the convoluted tubules of the kidney.

III. Mechanism of Adrenalin Glycosuria, and Its Relation to Other Forms of Glycosuria.

This topic will be treated in three parts:

(a) Mechanism.
(b) Relation to non-diabetic glycosurias.
(c) Relation to diabetic glycosuria.

(*a*) *Mechanism.*

The glycosuric, like the muscular, effects of adrenalin are the result of peripheral stimulation. A central mechanism is ruled out by the negative results of splanchnicotomy. Hirayama disputed this view to some extent, for he claimed that both adrenalin and caffein glycosuria are prevented by nicotin injection. He interpreted his findings to mean that there may be other sympathetic paths from center to periphery besides the splanchnics; nicotin injection therefore differs from splanchnicotomy by blocking all paths, instead of merely one. But Starkenstein (3) proved that Hirayama's results were mistaken, and that nicotin poisoning does not prevent adrenalin glycosuria.

It is commonly stated that adrenalin causes glycosuria by action upon the sympathetic terminals. The statement really rests upon analogy with the demonstrated action of adrenalin upon the myoneural junction of muscle. Whether liver-cells, like muscle-cells, contain a "receptive substance" which is stimulated in adrenalin glycosuria, or whether the nerve-fibres

or some other peripheral nervous structure receives the stimulus, is unknown.

It is generally accepted that adrenalin causes hyperglycemia by an action upon the liver. The above-mentioned experiments of Velich, Lepine (3*A*), Frank and Isaac, Falta and Priestley, and Michaud point in this direction. Others have asserted that the muscles as well as the liver lose glycogen in adrenalin glycosuria; but this effect might be secondary rather than primary. Starkenstein (3) showed that rabbits after adrenalin injection may excrete more sugar than corresponds to the loss of liver-glycogen; but new-formation of glycogen might be the explanation. A very high importance would attach to any definite proof that adrenalin directly causes a breaking down of muscle-glycogen, for it would show that the toxic glycosuric action of adrenalin, contrary to its other effects, is not limited to structures with sympathetic innervation.

Like every form of glycosuria brought about through an intermediate mechanism, adrenalin glycosuria is characterized by a latent period, between the time of injection and the first appearance of sugar in the urine. In this respect it stands in sharp contrast with phloridzin. The delay is not related with delay of absorption of the injection, for adrenalin causes glycosuria as quickly when given subcutaneously as when given intravenously. Straub (2) and Ritzmann especially studied this latent period and other features in connection with the intravenous injection of adrenalin. Ritzmann expresses the opinion that adrenalin, as a nervous stimulus, sets in motion some chemical process, which requires some time for completion. His experiments with continuous intravenous infusion of adrenalin show a delay of half an hour or more from the beginning of injection to the first appearance of glycosuria.

Adrenalin glycosuria is the result of an over-production of dextrose, in consequence of an accelerated breaking down of glycogen. This was proved by Vosburgh and Richards, and again by Iwanoff. Macleod and Pearce (3) proved that injection of adrenalin into the portal circulation of a living animal is followed by increased glycogenolysis in the liver. Zuelzer (3 and 4) demonstrated such a process in perfusion experiments. When dogs were killed by bleeding and the livers perfused with normal dog-blood under fixed conditions, the gain in the sugar-percentage of this blood was as follows:

(*a*) With livers of normal dogs, 8.5–15 per cent.

(*b*) With livers of dogs at height of adrenalin glycosuria, 50–113 per cent.

(*c*) With livers of dogs at height of diabetes after pancreatectomy, 27–66 per cent.

There is however no ground for assuming that the cause of the increased sugar-formation is the same in adrenalin poisoning and in diabetes.

The process of accelerated glycogenolysis brought about by adrenalin may perhaps continue after death, as Zuelzer claims; but it must probably be inaugurated during life. Starkenstein (3) found that when normal livers are perfused with salt solution or defibrinated blood, the addition of adrenalin to the perfusion fluid is without influence upon the rate of disappearance of glycogen. He attributes the negative result to the early death of the peripheral nervous mechanism in the excised liver. As noted elsewhere, other authors have reported increased sugar-formation in such experiments, but the concentration employed was excessive; and the possibility exists that the sugar-formation in these cases may have resulted from a different process; *i.e.*, not the typical stimulation of a peripheral nervous mechanism, but a direct injury of the liver cells, on a par with that produced by a number of harmful substances.

Numerous attempts have been made to demonstrate a higher content of post-mortem diastase in the liver and blood after adrenalin injection. The subject was reviewed in Chapter II. The best opinion is that of Macleod and of Starkenstein, that adrenalin glycosuria stands in no demonstrable connection with increase of diastase in the body.

(*b*) *Relation of Adrenalin to Non-diabetic Glycosurias.*

Blum called attention to the similarity of the glycosuria produced by adrenalin and by piqûre, and suggested the possibility that the nervous impulse of the latter is transmitted not directly to the liver, but to the adrenals. A. Mayer (1) next proved that after removal of both adrenals, the sugar-puncture no longer produces glycosuria. Eppinger, Falta and Rudinger attempted further analogies between adrenalin and piqûre, and considered that the glycosuria from the latter is due to a discharge of adrenalin from the chromaffin system. Wertheimer and Battez (3),

working with cats, contradicted Mayer's findings in rabbits; for they obtained heavy glycosuria from piqûre after epinephrectomy. Watermann and Smit (see also Watermann) claimed to prove by tests of the peripheral blood by the Meltzer-Ehrmann method that its adrenalin content is increased after piqûre. But Kahn (1 and 3) showed the absence of any demonstrable increase of adrenalin under these conditions. Nevertheless, Kahn confirmed Mayer's discovery that piqûre causes no glycosuria after epinephrectomy; and in epinephrectomized rabbits, which may survive indefinitely, this refractory condition persists throughout life. Kahn and Starkenstein showed that the negative result of piqûre is not, as Schwarz supposed, due to lack of liver-glycogen, for epinephrectomized rabbits possess the usual glycogen supply. Kahn (2) furthermore found that the piqûre produces marked histologic changes in the medulla of the adrenals. The chrome-staining is nearly lost, the cells are poor in granules and full of vacuoles, and physiological tests show the adrenalin content greatly diminished. Cutting a splanchnic nerve protects the adrenal of that side from these effects of piqûre; but the result is perfect only on the left side, since the right adrenal is supplied from both splanchnics. Artificial rhythmic stimulation of one splanchnic causes intense glycosuria, but does not change the adrenal medulla in this manner. Kahn (3) found that during the heavy glycosuria following subcutaneous injections of adrenalin, no increase of adrenalin in the peripheral blood is demonstrable. Brücke confirmed the absence of adrenalinemia after piqûre. Kahn (5) has later claimed to demonstrate an increase of adrenalin in blood collected from the vena cava opposite the right adrenal after piqûre. Neubauer (4) has proved that the blood-pressure is elevated after piqûre.

Not only piqûre glycosuria, but all the forms resembling it, have been supposed to partake more or less of the nature of an adrenalin-glycosuria; *i.e.*, the central nervous stimulus is transmitted to the adrenals, and the glycosuria results largely from an over-production of adrenalin. Pollak (2) in classifying the forms analogous to piqûre, included stimulation of sensory nerves, salt-glycosuria, chloroform, morphin, strychnin, carbon monoxide and caffein. Starkenstein (3) confirmed by Kahn (5) showed that all asphyxial glycosuria belongs in this group. Cannon and Hoskins reported that asphyxia, and also electrical stimulation of the sciatic nerve, are followed by an increase of adrenalin in the blood.

Salt glycosuria is assigned a somewhat doubtful position by Pollak. Fischer's experiments serve to place it in the list due to central stimulation. Külz proved that cutting the splanchnic nerves prevents salt glycosuria. McGuigan (2) has stated that after removal of the adrenals in rabbits, salt glycosuria remains absent; but in dogs, though epinephrectomy makes salt glycosuria more difficult, it can be produced. Removal of the adrenals in cats seems to have no effect upon salt glycosuria. Freund considers that salt and adrenalin are similar as respects curve of glycosuria, curve of temperature, and substances which inhibit their action. Watermann and Smit claimed the presence of increased adrenalin in the blood during salt glycosuria, but the claim is probably to be rejected along with their findings after piqûre.

Adrenalin is evidently not the agent which gives rise to cold-glycosuria. Although Reicher obtained positive Meltzer-Ehrmann reactions from the blood of animals subjected to cold, it is not certain that the mydriatic substance here was adrenalin. Loewit demonstrated the absence of adrenalinemia in the cold-glycosuria of frogs.

The similarity between the action of drugs of the caffein group and of piqûre has been demonstrated clearly. Pollak (2) proved that caffein glycosuria is prevented by splanchnicotomy. Nishi (1*A*) found that diuretin fails to cause glycosuria after:

(*a*) Cutting both splanchnics.
(*b*) Cutting the left splanchnic alone.
(*c*) Removal of both adrenals.
(*d*) Extirpation of right and cutting all nerves to left adrenal.
(*e*) Complete enervation of both adrenals.

On the other hand, diuretin still produces glycosuria after:

(*a*) Cutting right splanchnic.
(*b*) Extirpation of either adrenal.
(*c*) Cutting all adrenal nerves except from right coeliac ganglion to right adrenal.

Nishi therefore draws the conclusion that the central stimulus resulting from diuretin is transmitted not to the liver, but to the adrenals; so that diuretin is an adrenalin glycosuria. Miculicich has, however, established a distinction, by showing that hirudin inhibits adrenalin glycosuria but not diuretin glycosuria.

Pollak assigned a somewhat doubtful position to emotional glycosuria. It has been brought into relation with adrenalin by experiments from Cannon's laboratory. Cannon and de la Paz, using the intestine-strip test, determined an increase of adrenalin in the blood of a cat frightened by a dog. Cannon, Shohl and Wright found that though normal cats easily show glycosuria when tied, the epinephrectomized animals excrete no sugar even after much longer tying. My own experience has been similar. Elliott (2) induced in cats a mental state interpreted as extreme fright, by means of morphin or β-tetrahydronaphthylamine, and observed that the adrenalin of the adrenal medulla was thus exhausted.

Macleod and Pearce (3) measured the rate of glycogenolysis by the sugar-content of the blood of the vena cava opposite the liver. Electrical stimulation of the left splanchnic nerve produced in normal animals an increase of glycogenolysis. The removal of the left adrenal sufficed to prevent this effect, likewise ligation of the veins of both adrenals. Direct electrical stimulation of the hepatic plexus causes glycogenolysis in normal but not in epinephrectomized animals. When the hepatic artery and plexus were cut and the wall of the portal vein cauterized to destroy any possible nervous communication of the liver, stimulation of the splanchnic nerve produced little or no increase of sugar, but injection of a rather strong solution of adrenalin into the portal vein produced hyperglycemia.

Grek has made the latest study of the glycosuria following electrical stimulation of the splanchnic nerve, and classifies it as adrenalinogenic.

Reichenstein (2) observed that in human patients with a tendency to alimentary glycosuria, this tendency is increased by adrenalin. Individual diabetic patients were found to vary in their reaction to adrenalin. The author suggested an explanation on the basis of the supposed balance between the sympathetic and autonomic nervous systems. But the increased tendency to alimentary glycosuria is merely an example of the common law of summation of effects of glycosuric agents, with the usual variations of tolerance between diabetic patients.

The brilliant discovery of adrenalin and its striking physiological effects created such a powerful impression and gave such a stimulus to imagination, that the most varied important actions have been attributed to this substance, without very careful

scrutiny of the evidence. The fewer organs or secretions that are assumed to take a direct part in carbohydrate metabolism, the more easily comprehensible will this metabolism become, especially if the assumptions referred to happen to be incorrect. It is therefore worth while to examine the evidence for the supposed direct relations of adrenalin and the adrenals with the sugar economy. This inquiry may be undertaken in the following divisions.

1. Does adrenalin cause glycosuria?
2. Do the adrenals take part in carbohydrate metabolism?
3. Conclusions.

1. Does Adrenalin cause Glycosuria?

Throughout this writing, adrenalin glycosuria has been spoken of as if it were caused by adrenalin. This usage is justified by custom and convenience, and requires no change. But for the sake of accuracy, it is desirable to know whether the glycosuria observed is produced by the adrenalin itself. The evidence that it is a direct effect of the adrenalin itself consists essentially in (α) intravenous injections of adrenalin; (β) the picture of exhaustion of the chromaffin tissue after piqûre, etc.

(α) The physiological secretion of adrenalin corresponds to a continuous intravenous injection. The true effects of unchanged adrenalin should be best studied by such injection. Blum and some other authors [see Loewi (4), p. 1181] observed more or less glycosuria after such injections, but such glycosuria is generally slight, and most investigators have missed it altogether. Pollak (1) found that intravenous injection causes some hyperglycemia, but generally not enough for glycosuria unless diuresis is specially provided for. He attributed the absence of glycosuria chiefly to the oliguria following intravenous injection, but agreed that the subcutaneous method is far more effective. Macleod and Pearce (3) observed that injection of large doses of adrenalin into the portal circulation results in increased glycogenolysis in the liver. But the same is true of injection of almost any harmful substance, even air. Straub (2) discovered that the continuous intravenous infusion of a very dilute adrenalin solution regularly leads to glycosuria. Ritzmann followed up the method, and proved that, after a latent period, glycosuria begins and continues as long as there is an excess of adrenalin in the blood. He

held up the intravenous as the ideal method, on the ground that it imitates the natural secretion, and that a given quantity of adrenalin intravenously produces as much sugar-excretion as five times the quantity given subcutaneously. Ritzmann's results appear like a definite proof of the glycosuric action of adrenalin itself, but in strict criticism they are open to the following objections.

(I) The correspondence of the glycosuria to an increased adrenalin content of the blood is not decisive, for numerous authors have proved that adrenalinemia is not necessarily accompanied by glycosuria. If deficient diuresis were the only difficulty, the hyperglycemia produced by this direct intravenous introduction of large doses of the supposed effective agent should be enormous; but it is not.

(II) Straub (2) calculated that 94 per cent of a subcutaneous dose of adrenalin is destroyed. From the total or relative absence of the well-known pressor effects of adrenalin, it must be agreed that much or all of such a dose is destroyed or changed somehow. Yet Underhill (4) repeated Ritzmann's work, and proved conclusively that the former established idea is correct, viz., that the same dose of adrenalin injected subcutaneously produces greater glycosuria than when injected intravenously. During the glycosuria resulting from the subcutaneous injection of adrenalin, tests of the blood show no adrenalin increase [Falta and Priestley. Kahn (3)]. In human patients, when increase of pressure follows the subcutaneous injection, the curves of pressure and of glycosuria are not parallel [Falta, Newburgh and Nobel].

(III) Ritzmann did not in fact imitate the natural secretion of adrenalin as supposed. The disturbing element of the anæsthetic was demonstrated by Underhill. But it should further be called to attention that the normal secretion of adrenalin is not accompanied by an intravenous injection of one hundred to several hundred cubic centimetres of salt solution [in rabbits!]. This salt solution of itself would seldom produce glycosuria, but its effect upon an existing glycosuria is certainly great.

(IV) Glycosuria begins about half an hour after injection, whether the injection is subcutaneous or intravenous. Adrenalin is known to be quickly destroyed or changed in the blood and tissues. With subcutaneous injection, it is a possible hypothesis that glycosuria results from decomposition-products of the adrenalin, and such a possibility is not excluded with intravenous injection, for there is plenty of time for the decomposition to take place.

(β) The picture of exhaustion shown by the chromaffin tissue after piqûre and similar agencies has been mentioned. The protection afforded by nerve-section will be discussed under (2α), below. This picture of exhaustion has been interpreted to mean an intense discharge of adrenalin from the adrenals, and the consequent increase of adrenalin in the blood has been supposed to produce or aid powerfully in producing the glycosuria. The following considerations apply.

(I) The claim of Watermann and Smit of having demonstrated such an adrenalinemia was overthrown. Lately Kahn (5) has claimed to demonstrate after piqûre an increase of adrenalin in the serum from the vena cava opposite the right adrenal. But O'Connor has asserted that tests of the serum are not reliable to distinguish such differences. Especially, such an investigator as G. N. Stewart, using serum, was able to demonstrate an increase of adrenalin in the blood of the adrenal veins during splanchnic stimulation, but in the caval blood opposite the adrenal veins no such increase was demonstrable, because the dilution was too great. The alleged increase of adrenalin is therefore at least questionable. There is the anatomical evidence of an extremely abnormal condition in the adrenal, and the possibility that an abnormal kind of secretion is discharged. Granting that adrenalin reaches the blood in excess, the above criticisms concerning intravenous injections apply; it is not certain but that toxic decomposition products cause the glycosuria.

(II) Starkenstein (3) proved that a picture of exhaustion in the adrenal medulla, identical with that following piqûre, is produced by asphyxia or by carbon monoxide. Kahn (5) has confirmed the carbon monoxide findings. By reference to Chapter XII, it will be found that carbon monoxide glycosuria is slight and very inconstant; it is generally present in meat-fed animals, but generally absent in carbohydrate-fed animals, however rich in glycogen. Starkenstein took care to feed his animals on meat in order to obtain any glycosuria at all. Now, concerning the supposed relations of adrenalinemia, chromaffin exhaustion, and glycosuria, the following conditions, already mentioned, may be placed in parallel.

1. Intravenous injection of adrenalin. Marked demonstrable adrenalinemia. Generally no glycosuria unless a large quantity of salt solution is injected intravenously at the same time. When it occurs, glycosuria is less than after subcutaneous adrenalin injection.

2. Subcutaneous injection of adrenalin. No demonstrable adrenalinemia; no pressor effects. Intense glycosuria.

3. Piqûre. Intense glycosuria. Exhaustion of adrenal medulla. No demonstrable adrenalinemia in peripheral blood; increase of adrenalin in blood of adrenal veins claimed by Kahn.

4. CO poisoning. Glycosuria slight or absent. Exhaustion of adrenal medulla as after piqûre.

5. Direct stimulation of splanchnic nerves. Increase of adrenalin secretion. Considerable glycosuria. No picture of exhaustion in adrenal medulla.

The fact may also be mentioned that in Dog 18, after a puncture in the closed portion of the medulla just below the calamus, I observed typical extreme exhaustion of the adrenal medulla microscopically, without a trace of glycosuria. Since it is well known that by suitably placed punctures, fibres to the kidney may be stimulated with little or no stimulation of the liver, it may be worth investigating whether it may not also be possible to find areas where puncture regularly produces the typical adrenal discharge, with little or no glycosuric effect.

2. Do the Adrenals take Part in Carbohydrate Metabolism?

Adrenalin has sometimes been referred to as "the carbohydrate-mobilizing hormone" and as the substance "which maintains the sugar-tonus just as it does the muscle-tonus," etc. Such statements are at least unsupported. As previously mentioned, adrenalin does not maintain the muscle-tonus; and neither the asthenic and other symptoms, nor the hypoglycemia and glycogen-loss, following epinephrectomy are due to lack of adrenalin. The considerations under (1) render it doubtful whether adrenalin causes glycosuria. But there is a broader question possible, whether the adrenals through adrenalin or some other secretion, or in any other way, normally or abnormally play any part in the carbohydrate economy. The evidence pertains to (α) nerve-section and (β) epinephrectomy.

α. Nerve-Section.

When a central stimulus produces adrenal exhaustion, it is to be expected that section of the nerves will protect against this change; and Kahn and Starkenstein have found this to be the case. The nerve-section which protects the adrenals also pre-

vents glycosuria. The work of Nishi (1*A*) with cutting of different nerves was mentioned above, also that of Macleod and Pearce (3). The net result of this work is that nervous stimuli sometimes fail to cause hyperglycemia when prevented from reaching the adrenals, even though the path to the liver be open. As mentioned under (β) below, it is possible for glycosuria to occur sometimes under these conditions. When the nervous stimulus is allowed to pass to the adrenals, but prevented from reaching the liver, glycosuria may also occur, though it is diminished. It seems established therefore that under abnormal conditions, either adrenalin or some toxic substance discharged from the adrenals may produce some degree of glycosuria. Splanchnic stimulation — which does not produce the abnormal picture in the adrenals, although it does increase adrenalin secretion — does not produce hyperglycemia under these conditions (Macleod and Pearce).

Kahn (5) objected to the results of Macleod and Pearce, that after section of the structures except the portal vein, the liver is no longer an intact organ. The same of course applies to all these operations. It is quite possible that the cutting of nerves does more than block the stimulus; it may introduce unknown complications. O'Connor (2) found that splanchnicotomy greatly diminishes or abolishes the secretion of adrenalin; but his conclusion that this indicates a constant nervous stimulation does not necessarily follow, for the shock might throw the adrenals temporarily out of function. No one has tried the experiment of cutting the adrenal nerves, and performing piqûre after the animal has fully recovered. [Compare with the results of pancreatectomy and cord-section, by Hedon.] It is possible to consider that section of the adrenal nerves amounts to a temporary epinephrectomy from this standpoint.

β. Epinephrectomy.

Double epinephrectomy ordinarily prevents glycosuria from central or peripheral nervous stimulation; as noted above, removal of the left adrenal alone may suffice for this effect. It is not the result of weakness or glycogen-loss; rabbits which survive double epinephrectomy retain normal liver-glycogen but are refractory to piqûre all their lives. But Starkenstein (3) proved that in an epinephrectomized rabbit, vagus stimulation still produces hyperglycemia, though not sufficient for glycosuria. The results of Nishi were not quite as clean-cut as appears from the brief sum-

mary, for hyperglycemia occurred in some cases. Wertheimer and Battez (3) found that in cats, piqûre still produces heavy glycosuria after epinephrectomy. The view that piqûre causes a pure adrenalin glycosuria is no longer maintained. Kahn (5) admits the importance of the direct nervous stimulus.

Gautrelet and Thomas (2) proved that after double epinephrectomy, electrical stimulation of the left splanchnic nerve fails to produce glycosuria. They therefore explained Mayer's finding of the negative results of piqûre after epinephrectomy, as being due to inability of the splanchnic nerves to transmit the stimulus. Furthermore, Gautrelet and Thomas (3) demonstrated a diminished excitability of the entire sympathetic system after epinephrectomy. In epinephrectomized rabbits, the vessels of the ear are relaxed though relatively bloodless, and fail to respond to either heat or cold. Stimulation of the depressor nerve produces no lowering of blood-pressure. In epinephrectomized dogs, stimulation of the vago-sympathetic trunk causes mydriasis less easily than in normal animals. Electrical stimulation of the splanchnic not only fails to cause glycosuria, but the vaso-motor effects are also absent (tested 5 hours after epinephrectomy). Stimulation of the central end of the sciatic produces no elevation of blood-pressure.

3. Conclusions.

It is a justifiable assumption that the entire splanchnic system constitutes one harmonious mechanism. Stimulation or inhibition of central origin is not transmitted solely to one organ, but rather produces coöperative changes in all. Thus, glycogenolysis, adrenal discharge, and diuresis are produced by the direct nervous stimulus of the piqûre. The one demonstrated function of adrenalin is to assist the tone of the sympathetic system. It is fair to assume that increased sympathetic tone and increased adrenalin discharge, diminished sympathetic tone and diminished adrenalin discharge, go together. Under anatomically demonstrable abnormal conditions, the adrenal medulla may discharge enough toxic substance to produce glycosuria. The integrity of the adrenals is highly important for the production of glycosuria by nervous stimulation. Do these facts under abnormal conditions indicate that the adrenals take part in normal carbohydrate metabolism?

The abnormal discharge which exhausts the adrenals is on a par with a subcutaneous or intravenous adrenalin injection; it

merely shows that the adrenals contain enough toxic material for the purpose, without proving whether this material is adrenalin or abnormal products. Neither normally nor in disease has this anatomical picture ever been found spontaneously occurring in the adrenals. Epinephrectomized rabbits maintain an apparently normal carbohydrate metabolism. Hoskins showed that the effects of adrenalin upon the intestine may be directly opposite, according to the concentration employed. Therefore, the fact that adrenalin or related substances, being powerful nerve-poisons, may in toxic concentrations produce glycosuria, does not prove that these substances in the normal concentration play this or any other part in normal metabolism.

Through increased or diminished sympathetic tone, the adrenals presumably have a share in the nervous regulation of the liver. But is there anything special about this influence? Epinephrectomized rabbits are permanently refractory to piqûre; but what of the effects besides glycosuria? is there diuresis? is there salivation? Subcutaneous adrenalin injection normally produces diuresis; but Bierry and Mme. Gatin-Gruzewska found that in epinephrectomized rabbits it produces anuria; here is evidently an alteration of the nervous reaction of the kidneys due to epinephrectomy. The adrenals are necessary for normal sympathetic tone, and through this and through unknown functions they probably influence every organ in the body. But this well-demonstrated, general effect, applying to all sorts of functions, is a different matter from a specific rôle as a "sugar-mobilizing hormone," or as an antagonist of the specific internal secretion of the pancreas.

Ontogenetically and phylogenetically, the chromaffin tissue is practically a part of the sympathetic nervous system; the ganglion-cells in lower species produce their own adrenalin. Anatomically, if the chromaffin cells have a special relation to the carbohydrate economy of the liver, it would seem a very clumsy arrangement which places them where they discharge into the peripheral blood traces of a highly labile secretion, which must make the entire round of the tissues that destroy it, before a small portion through the hepatic artery and portal vein finally reaches the liver. Physiologically, it is not demonstrated that adrenalin within the normal limits of concentration in the systemic blood has any effect upon carbohydrate metabolism. Under abnormal experimental conditions, the most striking fact is the non-parallelism between

glycosuria and the other well-known effects of adrenalin. Therefore, all the evidence seems to suggest that neither adrenalin nor the chromaffin tissue has any specific rôle in carbohydrate metabolism. The nervous system governs various processes of metabolism; but there is as yet no proof that adrenalin through the sympathetic nervous system has normally any more effect upon carbohydrate than upon protein or fat metabolism, or upon diuresis or any other function under sympathetic control; the accidental fact that toxic doses of adrenalin happen to cause glycosuria should not create confusion on this point. It may simplify conceptions both of adrenalin and of carbohydrate metabolism to believe that the chromaffin tissue is merely the handmaiden of the sympathetic system, and that through its secretion adrenalin it has just one function, viz., to asist in the tone of the sympathetic mechanism. Probably many persons feel that simply because chemists were able to pounce upon, identify and isolate it, this one little hormone has been very much over-worked in recent literature, and it should not be called upon to perform too many varied functions. It is possible that at some time in the future, the eager investigation whether some forms of glycosuria due to sympathetic excitation happen to be accompanied by a demonstrable increase of adrenalin in the blood, may appear less important than at present.

(*c*) *Relation of Adrenalin to Diabetic Glycosuria.*

The idea that adrenalin glycosuria is in some way related with diabetes has been frequently expressed. Blum was attracted by it, Metzger accepted it, and Herter and Richards undertook to support it experimentally. The latter authors found intense glycosuria after painting the pancreas with adrenalin, and lesions of the islands of Langerhans in exceptional instances after fatal adrenalin injections. The accidental character of the insular lesions was admitted by Herter and Wakeman, all the phenomena are now known to be non-specific, and the reason why these experiments are so frequently quoted in text-books is not apparent. Noel-Paton (1) at first considered that glycosuria probably results from diminished utilization of sugar, due to toxic action of adrenalin upon the pancreas, but his later experiments (2) caused him to reverse his opinion. Blum and numerous later workers tried the effects of prolonged treatment with adrenalin; as previously mentioned, the result is not increase but disappearance of the

glycosuric effects. Lazarus claimed increase of the islands of Langerhans from repeated adrenalin injections in guinea-pigs. But Tiberti (3) found that intraperitoneal injections of adrenalin for 2–4 months were without effect upon the pancreas. Herxheimer [ref. by Cecil (4)] continued the injections for five months, with negative results.

Zuelzer's idea that diabetes and adrenalin glycosuria are identical is well known, and is merely an extreme form of the widespread polyglandular doctrine. Writers of this school seek to distinguish a pancreatic element and an adrenal element in diabetes, and suppose that the disease results from disturbance of a hypothetical "balance" between the pancreas and the chromaffin tissue. If adrenalin sets up anything like a temporary diabetes, there are just two possible mechanisms to consider. Either (1), adrenalin acts upon the pancreas, or (2), adrenalin acts upon the internal secretion of the pancreas.

(1) Adrenalin might conceivably act upon the pancreas by injuring its cells directly, by inhibiting their activity through nervous influence, or by somehow preventing the internal secretion from reaching the circulation. In any such event, adrenalin poisoning would be equivalent to a temporary, bloodless removal of the pancreas, and adrenalin glycosuria would correspond to a transient diabetes. That this is not the case, is proved by the following evidence.

(α) Glycosuria may begin within half an hour after injection of adrenalin. Extirpation of the pancreas, with all its associated trauma, has never been reported to cause glycosuria within a shorter period than 1½ hours; generally longer. Granting therefore that a small dose of adrenalin may be as effective as a total ablation of the pancreas, there is still no explanation for the early onset of the glycosuria.

(β) Adrenalin glycosuria occurs in absence of the pancreas. Noel-Paton observed it in depancreatized ducks and geese. Doyon, Morel and Kareff witnessed increase of blood-sugar in depancreatized dogs from adrenalin. Velich found that depancreatized frogs show no glycosuria till 1 to 3 days after the operation, but an injection of adrenalin after removal of the pancreas produces glycosuria in less than 5 hours; any of the other abdominal viscera may likewise be removed, without any effect upon adrenalin glycosuria, so long as the liver is left; but removal of the liver prevents glycosuria. Eppinger, Falta and Rudinger (1)

proved that adrenalin increases the glycosuria of depancreatized dogs. Frank and Isaac (4) state that adrenalin acts even more powerfully in the depancreatized than in the normal animal. This statement is doubtless true, owing to the looser binding of carbohydrate in diabetes. The entire evidence shows conclusively that adrenalin glycosuria is not the result of any action upon the pancreas.

(2) Adrenalin might conceivably act upon the internal secretion of the pancreas, by neutralizing, precipitating or destroying it; or especially, since adrenalin is imagined to "mobilize" carbohydrate, it might break up the combination of sugar and amboceptor. This hypothesis is more plausible than the other; for by acting upon the pancreatic secretion, adrenalin might produce glycosuria sooner than the actual extirpation of the pancreas. Here again, adrenalin glycosuria would represent a temporary diabetes. By some sort of action of adrenalin upon the internal secretion of the pancreas, the supply of this secretion supposedly becomes deficient, just as in diabetes, and glycosuria of a diabetic nature results. But again, the occurrence of adrenalin glycosuria after extirpation of the pancreas excludes such a possibility.

If adrenalin glycosuria is in any respect a temporary diabetes, this diabetes while it lasts is not mild; it is a *diabetes gravis*, with intense glycosuria on meat diet or even after considerable starvation. Since polyuria generally accompanies the glycosuria, a diabetic element is suggested. But there are two positive means of deciding the question. One is the dextrose paradox, and the other is the diuretic action of dextrose.

In this connection, an important experiment is that of Underhill and Closson (2). A dog of 8-kilo weight, on fixed diet, received 20 cc. adrenalin solution subcutaneously, and excreted 11.5 g. dextrose in the urine. Two days later the same dose of adrenalin was injected, and also 7 g. dextrose per kilo in 30 per cent solution. In the urine was found 17.6 g. dextrose. The authors rightly interpret this experiment as proving the power of the tissues to utilize dextrose during adrenalin poisoning, and as setting off adrenalin glycosuria in sharp contrast to diabetes.

Wilenko (4) has recently found that in adrenalin hyperglycemia, the respiratory quotient is not raised as after administration of dextrose. Also, during adrenalin glycosuria, dextrose given orally or subcutaneously failed to raise the respiratory quotient. Furthermore, intravenously injected dextrose was

more than quantitatively excreted; the following table shows the typical result, the dextrose injection being 1½ hours after the adrenalin injection.

	Glucose, intravenously.	Adrenalin, subcutaneously.	Urine.
Rabbit 42	1.4 g.	....	Sugar-free.
	.....	1 cc.	190 cc., with 3.8 g. sugar.
	1.4 g.	1 cc.	548 cc. with 5.4 g. sugar.

Wilenko therefore assigns to adrenalin a specific action of diminishing the glycolytic power of the organism. The following remarks are applicable.

(α) As previously noted in this chapter, there is poor agreement between different studies of the respiratory quotient in adrenalin poisoning. But Hari, and Fuchs and Roth, found evidence of an increased combustion of carbohydrate. It would seem that the effect is less marked or less constant in adrenalin hyperglycemia than in alimentary hyperglycemia, and it might be interesting to know the reason. Vasomotor changes are an interesting suggestion by Wilenko; changes in the permeability of the vessels are possible; and it is conceivable that other processes brought about by adrenalin mask the increased sugar-combustion.

(β) Orally or subcutaneously administered dextrose was found not to alter the quotient; but there is no proof that the dextrose was absorbed. Since adrenalin has been found to delay the absorption of strychnin or physostigmin so that the fatal outcome is postponed for 4 hours or the animal even recovers, there is a question possible concerning dextrose within the time-limits of Wilenko's experiments.

(γ) The results with intravenous injection of dextrose represent one of the numerous misapprehensions in the literature arising from failure to recognize the elementary laws of the behavior of sugar. These results have no reference to the glycolytic power. They come under two simple laws; (*a*) the summation of effects of glycosuric agencies; in a large proportion of cases, the sugar-excretion produced by any two agencies acting together is greater than the sum of the excretion produced by their action separately; (*b*) the increase of sugar excretion by diuretics; the

quantity of urine was in each case increased by the dextrose injection; a similar injection of saccharose or NaCl would produce a similar increase of dextrose excretion. Wilenko's mistake consists in having used such a small dose, falling within the limits of the above laws and giving the impression of a quantitative excretion. If he had used larger doses he would have found a very satisfactory power of utilization; and by progressively increasing doses it can be shown that the paradoxical law holds as usual. Adrenalin increases the sugar excretion, because it is a glycosuric agent and also (subcutaneously) a diuretic. The apparent tolerance is lowered. But the real tolerance remains infinite as always in non-diabetic conditions; increase of dose is all that is necessary to increase the assimilation. Furthermore, if the respiratory quotient were followed during intravenous injection of suitable quantities of dextrose, it would presumably be found that adrenalin will not abolish the effect upon the respiratory quotient, and thus the contrast with diabetes will be further evident.

In my own experiments, the Parke-Davis $\frac{1}{1000}$ solution of adrenalin chloride was used. In Dog 21 (weight 7640 g.) on July 31 a subcutaneous injection of 5 cc. of this solution was given, and two hours later an intravenous injection of 100 cc. 25 per cent dextrose solution. The existing glycosuria, due to adrenalin, was increased, but the total excretion following the dextrose injection was 11.71 g. On August 4, a similar intravenous injection of dextrose, without adrenalin, caused an excretion of 9.3 g. By varying the dosage of adrenalin and of dextrose, variations of these relations will be obtainable, the proportional excretion being of course greatest when the dose of adrenalin is large in comparison with the dose of dextrose; but all that is necessary is to increase the dose of dextrose in order to demonstrate the retained power of assimilation.

The record of Dog 17 (see protocol) shows that on March 9, $\frac{4}{5}$–$\frac{5}{6}$ of the pancreas was removed, and the dextrose injections of March 24 and 27 (Chapter VI) show how the tolerance was reduced. March 29 to April 3, the diet contained all the sugar that could be put into it; the feed was entirely cake-bakery scraps, consisting of sweetened cakes with sugar-icings, and in addition 200 cc. of 50–80 per cent sugar solution was given by tube daily. Then, on April 3, the dog received 100 cc. 50 per cent glucose solution by stomach tube, 100 cc. 20 per cent glucose solution subcutaneously, and 3 mg. adrenalin subcutaneously, all between

9 and 10 a.m. Up to 5 p.m. the glycosuria was heavy; but from 5 to 9 p.m. it was very slight, and the urine after 9 p.m. was negative. In this predisposed animal, therefore, the combined effects of adrenalin and maximum doses of sugar caused not the slightest tendency to persistence of the glycosuria. There is no sign of interference with the pancreatic function.

Since adrenalin injections spoil the appetite, this same animal was subjected to a series of fast-days for purposes of comparison. The results shown in the record may be summarized as follows.

May 29, 24 hours starvation. Drank 115 cc. water. Urine 79 cc.

June 5, 24 hours starvation. Subcutaneous injection of $4\frac{1}{2}$ mg. adrenalin. Drank 355 cc. water. Urine 347 cc., containing 3.42 g. sugar. In the record it is noteworthy that the urine-specimens containing the most sugar are smallest in volume, *i.e.*, the opposite of the rule in diabetes.

June 16, 24 hours starvation. Subcutaneous injection of 5 mg. adrenalin and 80 g. dextrose. Drank 1450 cc. water; vomited 765 cc.; retained 685 cc. Urine 231 cc., containing 15.79 g. sugar. In other words, most of the dose of dextrose was assimilated, and the dextrose acted as an anti-diuretic; for the drinking was more than on June 5 and the urine was less. Not until June 18 did the secondary polyuria appear.

The adrenalin may have delayed absorption, but the intense glycosuria proves that considerable absorption occurred. In view of the heavy drinking, the accumulation of water at the site of injection does not suffice to explain the absence of diuresis with a glycosuria as high as 12 per cent; as shown in Chapter VI, such a thing is impossible in diabetic dogs; and the percentage of sugar here is as high as in diabetic animals. Results of this sort, with adrenalin and with phloridzin, show that the difference between the diuretic behavior of dextrose in diabetic and non-diabetic animals is not a mere matter of quantity of sugar excreted. Incidentally, a diuretic action of adrenalin is still manifest here, for the urine-specimens of 70 cc. at 1 p.m. and 60 cc. at 3 p.m. on June 16 are larger than would ever be found after such a dose of dextrose without adrenalin. But as usual in non-diabetic glycosuria, the smallest specimens of urine contained the highest percentages of sugar. Here again, by varying the doses, differences of assimilation and of diuresis will readily be obtainable. But the paradoxical law and anti-diuretic action of dex-

trose are always demonstrable during adrenalin poisoning, even in animals on the verge of diabetes from partial pancreatectomy. Adrenalin does not "inhibit" nor "antagonize" the pancreas nor the internal secretion of the pancreas. The possibility may suggest itself of treating suitably predisposed animals with adrenalin for considerable periods, in the attempt to produce diabetes. The result will doubtless be a gradual production of "immunity," of renal origin, just as in normal animals. Adrenalin glycosuria is a simple toxic glycosuria. There is no evidence that it has any greater significance for either normal or diabetic conditions than the skin-necrosis which is produced by the same toxic doses. The adrenals have no direct connection whatever with diabetes.

In the closing paragraphs of this chapter, it is desired to turn from matters which have no significance for diabetes, to call closer attention to a subject which is of the deepest significance for the adrenals, diabetes, and general physiology. This subject is the mystery of the adrenals. For some reason, the pancreas has been made the field of dispute, and writers have asserted that they will not be convinced concerning its internal secretion till some pancreatic product modifies diabetes. The adrenals are accepted as typical organs of internal secretion. But yet, aside from adrenalin, we know practically no more about the adrenal function than Addison; and adrenalin does not explain. Otherwise, the evidence for an internal pancreatic secretion is better than for an internal adrenal secretion; adrenal grafts preserve an animal's life, and pancreatic grafts prevent diabetes; in addition, there are Forschbach's parabiosis experiments, and my experiments concerning diuresis may be interpreted in favor of an internal secretion of the pancreas. For convenience, the discussion of adrenal grafts is deferred to Chapter XVIII; but the mystery of the adrenals may be summarized here as follows.

(*a*) Animals survive epinephrectomy in apparent health, if they possess accessory adrenals, which are composed entirely of cortical tissue. These accessory adrenals may be scattered anywhere, even as far away as the epididymis.

(*b*) Adrenal grafts maintain an animal in health after epinephrectomy if they contain medullary in addition to cortical tissue. If they consist only of cortical tissue, the animal dies just as after simple epinephrectomy.

(*c*) Battelli and Stern performed continuous carotid cross-transfusion between an epinephrectomized and a normal animal; the former died with the usual symptoms; the latter remained normal and died only by bleeding to death into the other's vessels.

These experiments stand without question, and a little consideration shows how baffling is the situation which they create. It is a common supposition that the essential function of the adrenals is either to form an internal secretion or to distoxicate harmful substances; yet apparently (*c*) disproves this supposition absolutely. It may then be imagined that the explanation is in the nervous system; that local ganglia or plexuses are vital; but both (*a*) and (*b*) exclude this possibility. Some particular interaction between cortical and medullary tissue might be suggested by (*b*), but (*a*) shows that cortical tissue alone, remote from any medullary tissue, may preserve life. The subject assumes greater importance when it is found that this behavior is not peculiar to the adrenals. As mentioned in Chapter VII, Hedon has proved that in cross-transfusion of a normal and a depancreatized animal, the former remains normal, and the latter becomes diabetic on the table. How then shall either an internal secretory or a distoxicating function explain? Yet here again, a nervous explanation is not warranted; to attempt it would be an unjustified disregard of transplantation and parabiosis experiments, and would not help toward solving the analogous adrenal puzzle.

With respect to adrenalin, Lichtwitz attempted to prove that adrenalin travels along nerve-fibres, but his hypothesis was overthrown [see Bayer (*2*), pp. 34–35]. Lepine suggested the possibility of direct diffusion of adrenalin into neighboring structures; but the animal does not die for want of adrenalin, probably not for want of chromaffin tissue. Can any substance travel along nerves or by other unknown ways so rapidly? *e.g.*, the changes in the vessels of the rabbit's ear observed by Gautrelet and Thomas within a few hours after epinephrectomy. And if it is some such diffusion, why is an accessory mass of cortical tissue near the epididymis sufficient, and a graft in the kidney sufficient if it contains both tissues but not if it contains cortical tissue only? According to Forschbach's work, union by tissue prevents diabetes; according to Hedon's work, union by blood does not. But neither parabiosis nor cross-transfusion prevents death from epinephrectomy. Must it be imagined that some secretions are specific to the individual animal? Adrenalin seems to be the

same through many animal divisions, and thyroid similarly. Many biological characters are obviously peculiar to a species; and experiments with parabiosis, organ-transplants, etc., show that each animal has its individual distinction. But such complete auto-specificity as indicated by the transfusion experiments is not probable; and the problem of extracts is not thus solved, for an animal's own pancreas or adrenals injected into itself are as useless as those from other animals. Speculations of radioactive or equally abstruse influences of organ upon organ could hardly be absurd under the conditions. It seems possible that something is here, outside the present knowledge of physiology, as unexplainable as nervous phenomena before nerves were known, or as internal secretory phenomena before internal secretion was known. The most practical lesson seems to be that difficulties are not limited to the pancreas. There is evidence for an internal pancreatic secretion, even though this does not clear away all mystery. It is to be hoped that through the lines opened up by Battelli and Stern and by Hedon, the adrenals will contribute more than heretofore to the true understanding of diabetes.

CHAPTER XVII.

THE NERVOUS SYSTEM IN RELATION TO GLYCOSURIA AND DIABETES.

THE nervous system is universally recognized as the commonest cause of non-diabetic glycosuria, and this view is supported by an abundance of conclusive evidence, both experimental and clinical. Its relation to diabetes is not demonstrated, but an etiological rôle is assumed by practically all authors. Experimental evidence for this assumption is lacking, and it rests wholly upon interpretation of clinical observations. Though diabetes often occurs in conjunction with a general neurotic disposition, the majority, even of these cases, offer no clue as to whether the actual cause lies in the nervous system or elsewhere. The only real clinical evidence for the nervous etiology of diabetes consists in unusual cases, mostly of so-called traumatic diabetes. In only a few of such cases has the distinctive diagnosis been established beyond suspicion. Nothing like a satisfactory dividing line between traumatic diabetes and traumatic glycosuria has ever been drawn. If a purely nervous cause of true diabetes exists, it is not known whether it is concerned only in a small group of atypical cases, or whether these cases are typical of the disease in general, merely presenting in demonstrable form a relationship present but not demonstrable in the majority of diabetics.

As stated, most authors accept the nervous origin of at least a certain number of cases of diabetes. Pflüger was an extreme advocate of the etiological importance of the nervous system; such a position was all the more natural to him because he recognized no accurate dividing line between diabetes and glycosuria. Lepine [(1), p. 404 ff.] presents evidence for the existence of nervous diabetes. The relation of nervous cases to other forms of diabetes is occasionally discussed. Hoffmann and others have tried to make an actual separation between "nervous" and "constitutional" diabetes; a favorite supposition of such authors is that some nervous irritation keeps up a perpetual stimulation of the liver, similar to Claude Bernard's piqûre. The idea has however been dropped for lack of evidence. Von Noorden [(1), p. 74]

says: "It may be recognized with certainty that in human pathology acute neuropathogenic glycosurias exist, and that also the true diabetic glycosuria may be increased and diminished by nervous influences. On the contrary, it is at least doubtful and probably impossible that a true chronic diabetes can be permanently maintained solely by nervous influences, without functional or anatomic disease of the sugar-regulating organs. The first impulse may indeed proceed from the nervous system, *e.g.*, in the form of a powerful disturbance of equilibrium of the chromaffin system, and further shocks from nervous influences may follow. But if out of the transitory glycosuria there has developed a diabetes in the clinical sense of the word, then the disturbance set up in the regulating organs has developed into one which is independent of the primary injury. We indeed see the same thing in other organs, in the stomach, in the intestine, above all in the heart; primary injury by nervous influences, persistence and further development of the disturbances long after the nervous influences have ceased to act." Naunyn (p. 454 ff.) distinctly recognizes the nervous system as an important cause of diabetes. He proceeds from the statement, "Of the nervous system and of the pancreas it is certain that their disease can produce diabetes." After properly rejecting the influence of the adrenal and the thyroid as unproved, he says further (p. 456): "Concerning the way by which the disorder of the diabetogenic organ leads to diabetes, we know nothing at all certain except for the pancreas. For this organ it may be considered certain, that the blood in it normally undergoes a change which is essential for the normal course of sugar metabolism, and absence of which is manifested in the occurrence of diabetes; that the pancreas contributes to the blood a still 'unknown substance,' which is indispensable for the utilization of sugar. Important is the fact that this 'internal secretion' of the pancreas may alone suffer harm and diabetes thereby be produced, without the 'external secretion' of the gland being disturbed." Furthermore, Naunyn (pp. 457–58) attributes the diabetes following nervous disorders not to a direct action of the nerves themselves upon metabolism, but to their influence upon the function of certain organs, primarily the pancreas; and he draws the appropriate analogy between the disturbance in muscles resulting from interference with their nerve-supply, and the assumed disturbance in the pancreas resulting from interference with its nerve-supply.

In a consideration of this subject, the anatomical relations must be borne in mind. The nerves supplying the viscera concerned are essentially the vagus and the sympathetic. The vagus may have through its centripetal fibres the same reflex effect in producing slight glycosuria as any other sensory nerve. Falta (4 and 6) and the polyglandular school have chosen the vagus as the nerve of the pancreas, and thus set this supposed autonomic innervation over against the sympathetic innervation of the chromaffin system. On the contrary Frank and Isaac (2 and 4) assert that there is no autonomic nerve governing the internal secretion of the pancreas, and they uphold the view "possible since the time of Claude Bernard," that diabetes is a sympathetic neurosis. Though the vagus presides over the external secretion of the pancreas, there is no evidence that it has anything to do with the internal function.

Conceptions concerning the undoubted rôle of the sympathetic in producing glycosuria, and its possible influence in the development of diabetes, generally start from the so-called sugar-center discovered by Claude Bernard in the medulla. This is not a nerve-center in the proper sense of the word, but is an area within which certain sympathetic nerve-tracts can conveniently be stimulated for the production of glycosuria. The same tracts can be stimulated at other places, some of them very remote from the medulla. The possible importance of lesions of the Bernard center in the production of glycosuria in human patients therefore need not be denied, but on the other hand it is not necessary to attempt to measure the glycosuric importance of every lesion by the degree of its proximity to this so-called center. This holds, even if we assume that the mechanism of all these glycosurias is identical, as it may perhaps not be. For example, above the medulla it is possible that there are separate genuine nerve-centers for the liver, pancreas, adrenals, kidneys, etc. Lesions of these specific centers may produce highly specific results, and from many regions of the brain and nervous system, stimuli may affect these centers. At any rate, it is a fact that injuries in many different parts of the brain seem to be able to cause more or less intense and prolonged glycosuria. Within the medulla, all tracts necessarily lie close together, because the space is small. Moreover, we deal here with fibres from central organs, designed to control a group of related organs in harmonious functions, and it is natural that they should be closely associated in these tracts. It

seems evident that in puncturing the floor of the fourth ventricle, injury is produced of fibres controlling the liver, pancreas, adrenals, kidneys and all the organs of the splanchnic domain. The existence of separate fibres for the liver and kidneys is experimentally demonstrable, for by varying the site of puncture, it is possible to obtain glycosuria with or without polyuria, with or without albuminuria, and likewise polyuria without glycosuria. The stimulus of the typical puncture causes changes in the liver manifested prominently by glycogen-destruction, changes in the adrenals manifested prominently by exhaustion of the chromaffin cells, changes in the kidneys manifested prominently by polyuria; and it is a justifiable supposition that changes of some nature also occur in the pancreas.

The sympathetic tracts in question pass from the medulla into the spinal cord; stimulation of them here, and also of certain associated sympathetic bundles in the neck, causes glycosuria. The fibres emerge by the rami communicantes of the thoracic nerve roots at unknown levels, and with other sympathetic fibres enter the abdomen in the form of the splanchnic nerves; suitable stimulation anywhere along this path may cause glycosuria. The majority of the fibres end in networks about the ganglion-cells of the semilunar ganglia, and all the others presumably terminate similarly in connection with ganglion-cells somewhere in this region. The neuraxes of these ganglion-cells establish the direct communication with the various viscera. Stimulation of the fibres passing in the hepatic plexus to the liver may produce glycosuria.

The precise destination and function of the terminal fibres remains in doubt. It is universally acknowledged that the vasomotor function is highly important; that a large proportion of the fibres to each viscus terminate in connection with the smooth muscle fibres in the walls of its blood-vessels, and probably influence the function of the viscus to a considerable extent through this agency. But whether all the fibres terminate thus, and whether the function of the abdominal sympathetic is purely vasomotor, is a question still seriously disputed, with the preponderance of opinion varying with the individual organs.

As respects the kidney, the purely vasomotor hypothesis has its strongest following. I have made no attempt to follow the literature, except as it touches the question of glycosuria. Kossa (3) has opposed the prevalent view, by concluding that the renal

nerves act not only on the vessels but also on the parenchyma, influencing the permeability and regulating it. Stewart's text-book presents concisely the arguments in favor of the specific secretory as opposed to the mechanical theory of urinary secretion, but states that no secretory nerves have been demonstrated, and that changes in renal secretion which follow section or stimulation of the nerves can be explained by the variations in blood-pressure. Nevertheless, the termination of nerve-fibres upon the epithelial cells has been anatomically demonstrated, and it seems *a priori* doubtful whether such an important process as the secretion of urine is left entirely without direct nervous control.

For the liver, the existence of secretory nerves is more evenly debated, but with the advantage apparently in favor of the affirmative. While the question must be considered to include a number of hepatic functions, yet the sugar-regulating function is the one primarily of interest here, and has also been a favorite choice of investigators. The literature may well be followed by beginning with the work of Macleod for the affirmative and of Wertheimer and Battez for the negative. A portion of it was presented in Chapter II, in connection with diastases. Certain experiments of Chapter XX will add a trifle of evidence.

In the preceding chapter, the question of secretory nerves to the adrenals was discussed, and it was seen that the evidence strongly favors the existence of such nerves.

In approaching the pancreas, we as usual enter unknown territory. Information concerning the innervation of the islets is especially scanty. The statement of Cunningham's Anatomy concerning the nerve-supply of the pancreas is, "The nerves, which are almost entirely non-medullated, come from the solar plexus, through the coeliac, splenic and superior mesenteric plexuses." Böhm-Davidoff-Huber's text-book of histology treats the subject as follows. "The nerves of the pancreas have been investigated by Cajal and Sala, and Erik Müller, who find in this gland large numbers of non-medullated nerve-fibres, some coming from sympathetic ganglion cells situated in the pancreas and others entering from without. The non-medullated nerve-fibres form plexuses surrounding the excretory ducts and end in periacinal networks. Fibrils from the network about the alveoli were traced to the secretory cells. A portion of the non-medullated nerves in the pancreas form perivascular plexuses." Natus (2) was struck by the fact that between the layers of the mesentery

on both sides of the pancreas is a broad network of non-medullated nerve-fibres, which is not present in the mesentery elsewhere. After ligation of the duct, degenerative changes are said to occur in the nerves. Hedon (11) has presented evidence that the vagus is not even the sensory nerve of the pancreas. When a subcutaneous pancreatic graft is removed from a dog without anæsthesia, the animal shows signs of pain, especially when the pedicle is ligated and cut. But if the spinal cord has been cut between the seventh cervical and first thoracic vertebrae, thus interrupting the sympathetic paths, the operation upon the graft produces not the slightest sign of discomfort, though the vagi remain intact.

Gentes in 1902 made the first investigation of the nerve-supply of the islets. He found these structures in the rat richly supplied by means of a network surrounding them and giving off fibres to terminate between the cells. The rich nerve-supply in his opinion indicates an important function of the islets. Pensa in 1905, by the Golgi method, also demonstrated a rich network of nerve-fibres supplying the islets; the nerves were distributed along the blood-vessels and between the islet cells, and were different both in number and arrangement from the nerves to the acini. Various authors have noted the presence of nerve-cells and ganglia in the pancreas. The best general account of the nerve-supply is given by Laguesse (10). Zamboni found no changes in the pancreas in consequence of section of its nerves. Scaffidi has reported studies of cytological changes in the pancreas after resection and stimulation of the vagus and sympathetic. Unfortunately, all notice of the islets was omitted, and the paper deals entirely with alterations in the acinar cells. With the recent improvements in the methods of staining the islet cells, it is to be hoped that some research covering this point may be undertaken.

All that comes out of the discussion up to this point therefore is that the islets have a rich supply of sympathetic nerve-fibres derived from the solar plexus and from local ganglion-cells, and that there is nothing to indicate that they stand under the control of the vagus. Since both peripheral and central nerve-stimulation are able to produce characteristic phenomena in liver, kidney and adrenals, it is reasonable to suppose that similar stimulation may produce analogous phenomena in the pancreas, and — of special interest for our present subject — in the islets. Beyond

inherent probability, however, there is no evidence. No nerve-changes characteristic of diabetes are known. No diabetes has ever been produced experimentally by nervous means. Clinical nerve-injuries have been followed by true diabetes, but there is no proof that the effect of such injuries was upon the pancreas or its islets. The Bernard puncture is followed by glycosuria and presumably has some influence upon the pancreas, but three valid reasons rule out the pancreas as a factor in this glycosuria; (1) the glycosuria begins sooner than the glycosuria following even a total extirpation of the pancreas, and may be over and done with before a true diabetic glycosuria could be well started; (2) such extensive removal of pancreatic tissue is necessary to produce diabetes, that it is highly improbable that a single small nervous lesion could disable the gland to equal degree (and with partial extirpation, diabetes is generally delayed for several days); (3) piqûre produces its typical effects in totally depancreatized animals. If therefore the piqûre produces any effect upon the pancreas, we have as yet no proof of it. If any sort of nervous process whatever has any influence either to increase or to diminish the internal secretion of the pancreas, the fact has not been revealed nor even suggested by experimental evidence.

The above brief sketch has had reference primarily to the anatomical facts. It is now necessary to examine in greater detail the physiological evidence bearing on the question. Previous chapters have treated to sufficient extent the numerous glycosurias due to the action of chemical substances upon the nervous system. None of these has ever resulted in diabetes. The present chapter is to be devoted primarily to other forms of nervous stimulation, either by the usual experimental (especially operative) methods, or by the action of disease-processes involving the nervous system in human patients. Stimulation is in fact what is involved, for paralytic lesions (not to be confused with the irritative processes which may accompany them) have never been known to give rise to glycosuria. Instead of following the usual historical sequence, by beginning with the piqûre, the order for the present discussion will be anatomical. It will begin with stimulation of peripheral nerves, as being closest to the organs actually affected by the stimulation, and it will proceed upward along the nerve-paths to the brain-centers, and from these to the psychic causes of glycosuria. The distinction between direct and reflex influence can be followed to only slight extent. But glyco-

suria will be kept as distinct as possible from diabetes, and clinical and experimental evidence will be grouped separately. The arrangement accordingly becomes the following:

1. Glycosuria from stimulation of peripheral nerves.
   A. Experimental.
   B. Clinical.
2. Glycosuria of central nervous origin.
   A. Experimental.
   B. Clinical.
3. Glycosuria of psychic origin.
   A. Experimental.
   B. Clinical.

1. Glycosuria from Stimulation of Peripheral Nerves.

A. Experimental.

The glycosuria resulting from formal stimulation of isolated nerve-trunks by electricity, and by irritant drugs, such as croton oil, etc., has been described heretofore, chiefly in Chapter XII. It was found in general that suitable stimuli applied to certain efferent nerves, especially the splanchnics and the hepatic plexus, give rise to hyperglycemia, apparently by direct action upon the liver-cells. Also, stimulation of important afferent tracts, either in peripheral nerves or in the spinal cord, leads frequently to glycosuria, though asphyxia is supposed to play a part in its production. Here we need repeat only the facts that Froning was sometimes able to obtain reflex glycosuria lasting several days, and Starkenstein (3) observed reflex hyperglycemia from vagus stimulation after epinephrectomy. Though Bernard (2) observed no glycosuria from extirpation or laceration of one or both semilunar ganglia, Eckhard and Cyon and Aladoff discovered the glycosuria which results from operations upon the inferior cervical ganglion and certain of the sympathetic trunks in the neck. Lombroso (16) refers to the attempts of Lustig, Kaufmann, Marrassini and Zamboni to extirpate the solar plexus or destroy the pancreatic nerves; only transient glycosuria resulted. Grek has made the latest study of glycosuria and chloride excretion after electrical stimulation of the splanchnic nerves.

The glycosuria following various surgical operations has received considerable attention in diabetic literature. De Renzi and Reale reported glycosuria after removal of all the salivary glands in the dog, and looked upon the condition as true diabetes. Minkowski [(1), p. 56 ff] abundantly refuted this claim, and it must rank as a simple post-operative glycosuria due to nerve-irritation. Other glycosurias reported by various writers after operations upon various other organs have a similar status. On the other hand, the work of Rose and of Nishi (14) proves that even in as sensitive an animal as the rabbit, operations can be performed, involving even the cutting of important nerves, without glycosuria and without noteworthy hyperglycemia.

The form of glycosuria, due to peripheral nervous irritation, which aroused more discussion than any other was the so-called "duodenal diabetes" of Pflüger. Pflüger (13) — in casting about for some evidence of that which his insight told him must exist, viz., a nervous basis of diabetes — conceived the idea that the pancreas, which is embryologically an out-growth from the wall of the duodenum, continues throughout life to be controlled by nerves derived from the gangliated plexus in the wall of the duodenum. He tested the idea first in frogs, and reported that these animals, after extirpation of the duodenum and no injury to the pancreas except the supposed loss of its nerve-supply, showed a glycosuria persisting till death and even more intense than after extirpation of the pancreas. Likewise, complete separation of the duodenum and pancreas, by severing the mesentery between them, is said to have produced a similar glycosuria, though exceptions were encountered. Pflüger's attempts to reproduce these results in dogs were not encouraging, for a slight and transient post-operative glycosuria was all that was obtained. He at first attempted to excuse the failure on the basis of the prostration and early death of the dogs; later he fell back upon the early work of de Renzi and Reale. In an extended polemic, Pflüger (19, 20, 21, 22) defended his untenable position as well as possible against the attacks of Minkowski and others. Neither he nor de Renzi and Reale were able to reproduce the prolonged glycosuria which the latter authors claimed to have found, especially in one unusual instance, after extirpation of the duodenum in dogs. Pflüger in particular exhausted his ingenuity in producing nerve-injuries and setting up inflammatory and adhesive processes when the duodenum was removed, but without avail.

A few clinical and experimental reports seemed to support slightly the view of Pflüger. Zak described two human cases. One patient drank caustic potash; the glycosuria was 3.6 per cent; and autopsy showed corrosion of duodenal as well as gastric mucosa. The other patient drank nitric acid and died 36 hours later; here also the duodenum was involved, and there was glycosuria of 0.55 per cent. In another case of caustic potash poisoning, the injury was limited to the stomach, not extending to the duodenum; and here glycosuria was absent. A support of Pflüger's views, which seems implied in Zak's original article, was expressly denied by him in a later note. Herlitzka (1 and 2) produced glycosuria of several days duration in frogs by injection of nicotin-vaselin into the duodenum. The drug thus applied was supposed to paralyze the nerve-cells in the duodenal wall, and through them the pancreas. Similar injections of plain vaselin were claimed to be without effect; and the injection of nicotin subcutaneously (*i.e.*, remote from the duodenum) resulted in only slight, transient and uncertain glycosuria. In general he agreed with Pflüger, but considered that the effect was due not to centrifugal but to centripetal neurones. Eichler and Silbergleit, by laparotomy, injected caustic soda into the duodenum of dogs, or destroyed its mucous membrane with the Paquelin cautery. Slight glycosuria generally followed, but so did it after similar treatment of other portions of the intestine. They never obtained a lasting glycosuria. They looked upon the glycosuria as a mere expression of nerve-injury, and refused to accept the interpretation of "duodenal diabetes." Visentini (1 and 2*A*) extirpated the duodenum in dogs, and sometimes also removed the head and body of the pancreas and neighboring tissue, leaving only the splenic end of the pancreas. There was occasionally a transient post-operative glycosuria, frequently none. He opposed Pflüger. Reference may properly be made also to the experiments of A. Müller. These were conducted not with a view to diabetes, but to the production of paralytic ileus. For this purpose, he removed the musculature of the stomach and of different portions of the intestine of dogs. The operations were such as should produce extensive destruction of intestinal nerves, yet nothing like diabetes was reported.

The negative reports soon became overwhelming. Ehrmann (1) removed the duodenum in "a large number" of dogs; some of them showed no glycosuria, others merely a glycosuria below

1 per cent on the first day after operation. He concluded that ablation of the duodenum causes no diabetes. Lauwens reported to the same effect. S. Rosenberg (2 and 3) came to the conclusion that duodenal diabetes exists in neither dog nor frog. Tiberti (4 and 4*A*) extirpated the duodenum completely, performing a gastro-enterostomy and draining the bile to the outside of the body. The operation was severe, and the longest survival among his dogs was five days. There was no glycosuria. Cimeroni removed the entire duodenum and a third of the stomach in numerous dogs, with entirely negative results. Minkowski (5 and 7) brought the most decisive evidence, when he exhibited a dog in perfect health four weeks after total extirpation of the duodenum. Such an operation was shown to be followed by only a slight transient glycosuria. But when a total extirpation of the pancreas was subsequently performed in this same dog, the usual diabetes appeared in full intensity. Tscherniachowski also proved that after resection of the duodenum, glycosuria is either absent or very slight and transitory. Loewit (3) in a long and painstaking research was able to obtain diabetes in frogs by extirpation of the pancreas but not of the duodenum. The division of the mesentery and other methods of nerve-injury considered important by Pflüger likewise yielded negative results. He showed that it is not permissible in such experiments to keep the frogs on ice, as Pflüger had done, because of the liability to cold-glycosuria. The general conclusion therefore is that "duodenal diabetes" is non-existent. Pflüger was misled by glycosuria due to cold in frogs and to operative trauma in dogs.

The question of the influence of nerve-injuries in the production of diabetes by pancreatic operations was naturally one that presented itself to the earliest investigators. Thiroloix at first favored a nervous hypothesis, but experience with pancreatic grafts quickly made him a supporter of the internal secretory doctrine. Minkowski [(1), p. 30] mentions the transient glycosuria that may follow almost any surgical operation, but considers that it is more frequent and intense when the operation involves the pancreas or its neighborhood. In his own experience, of 32 operations of partial pancreatic resection, transplantation, ligation of ducts, or faradization of the bile duct, transitory glycosuria was encountered 15 times, and in some cases was as high as 4 or 5 per cent. Again (p. 33), he mentions an experiment of Thiroloix, in which the entire pancreas was dissected free and left

floating except for a single vascular pedicle. The dog died in three days and meanwhile excreted as high as 3 per cent dextrose. Von Mering and Minkowski believed that they ruled out the nervous factor by first, in one dog, isolating the pancreas completely from the mesentery, leaving it connected only with the duodenum, and then in another dog isolating it completely from the duodenum, leaving it connected only with the mesentery; and showing that diabetes developed in neither dog. Marcuse proved that if all the steps of the pancreatectomy operation are performed in frogs, except the actual removal of the pancreas, no diabetes results. As mentioned, Loewit's experience with nerve-injuries in the region of the pancreas was similar. Zamboni resected the pancreatic nerves in dogs; the operation is well borne and produces no diabetes, and at autopsy no changes are found in the pancreas. Underhill (1) concluded that the glycosuria resulting from painting the pancreas with piperidin is not the consequence of any specific effect upon the pancreatic cells. The same applies to painting the pancreas with adrenalin. Underhill showed that the pancreas may be painted with pyrrol, frozen by a spray of ethyl chloride, or handled roughly, without producing glycosuria. As already mentioned, Pflüger [(1), p. 472 ff] attributed some of Thiroloix's results to the supposed nerve-injuries associated with his method of operating.

If evidence is lacking that experimental injury of nerves has any influence in the production of diabetes, there is an equal absence of any indication that diabetes can be prevented by nervous influence. Cutting the splanchnics, enervation of the liver, etc., are without influence upon the course of events following pancreatectomy. Chauveau and Kaufmann considered that section of the spinal cord is a determining factor, and this idea contributed to the building up of their complicated doctrine. They found that division of the cervico-dorsal cord is followed by hypoglycemia (as Bernard discovered), and that subsequent removal of the pancreas produces no hyperglycemia nor glycosuria; on the contrary, the blood-sugar if anything falls lower. But if pancreatectomy is performed first, the resulting hyperglycemia and glycosuria are not abolished by the subsequent section of the spinal cord. It is one of Hedon's valuable contributions to have repeated this work under better conditions. Hedon (10 and 11) proved that although the above statements are correct, a delay until the initial shock has passed off alters the conditions com-

pletely. His method was to sever the cord between the last cervical and first thoracic vertebrae, then wait a few days till the animal had recovered somewhat, and then extirpate the pancreas. By an improved operative method, the cord was crushed rather than cut. A further improvement in several experiments consisted in extirpating the pancreas leaving a subcutaneous graft, then after recovery cutting the cord, and then a few days later removing the pancreatic graft, thus bringing on diabetes without subjecting the animal in its weakened condition to a major operation. In one case the final removal of the graft was not necessary, for its atrophy brought on a diabetes of the Sandmeyer type. In every instance, diabetes occurred precisely as in normal animals; the section of the cord produced no change whatever as respects its onset, course, or intensity. The absence of glycosuria, when pancreatectomy is performed within a few hours after section of the cord, is therefore due merely to the acute nervous shock.

Besides clearing up a troublesome point, Hedon's research is of interest as illustrating the fallacy of depending upon glycosuria as the sole test of diabetes. When the cervico-dorsal cord of an animal is divided, and the pancreas immediately removed, glycosuria remains absent during the brief period of life, but the animal is just as truly diabetic as if the cord had not been cut, or as if the pancreas had first been removed and then the cord cut. In the one instance, the disorder of metabolism resulting from the spinal lesion happens to express itself in the form of a paralysis of sugar-production, especially in the liver. An analogous condition is obtainable when the liver is removed, or when the dog is starved nearly to death before pancreatectomy, or when intense shock, infection or any other cause of prostration follows the operation. In every instance, it should be understood that the animal with diabetes plus paralysis of sugar-production is just as diabetic as the animal with diabetes alone.

As a digression, it seems desirable to notice here some interesting questions raised by Pflüger concerning the origin of certain well-known complications of diabetes, viz., the hunger and thirst. Two notions, to some extent mutually contradictory, were advanced by him. One was that polyphagia, polydipsia and polyuria are the signs of partial extirpation. He therefore persistently referred to Minkowski's extirpations as partial, and supported his contention by the absence of such symptoms in his own dogs (operated by Witzel), and in those reported by Sandmeyer and

by Schultz and Zuelzer. Minkowski retorted that Pflüger's dogs all had peritoneal abscesses, and that if one takes the trouble to remove the pancreas in two sittings, leaving only a small subcutaneous graft to be taken out at the second operation, it is possible to obtain totally depancreatized animals without peritoneal infection and with hunger and thirst characteristically exaggerated. Pflüger's other idea was that the symptoms in question result from irritation of "hunger and thirst nerves" in consequence of the operation. Obviously, according to this notion, these nerves ought to be fully as much irritated by total removal of the pancreas as by the operations in which Minkowski is claimed to have left a few pancreatic fragments of microscopic size. Minkowski (4) replied that in all the thousands of surgical operations in human patients and of physiological manipulations in animals, no sign of the existence of such alleged nerves of hunger and thirst had ever been found. The point thus brought into dispute involves not only the question why the diabetic dog is hungrier than the normal, but, back of that, the question why and how any animal experiences hunger.

Hedon (11) observed that a dog still shows desire for food and eats with relish when both the spinal cord and the vagi are divided, *i.e.*, when the brain is cut off from all possible communication with the abdominal organs. The experiment is not new. Also, Valenti performed experiments with cocainization of the upper alimentary mucosa, of the vagi, and of the gastric mucosa. He concluded that sensations of hunger and thirst originate in the mucosa of the pharynx, œsophagus and stomach, for local anæsthesia of these regions abolishes the sensations, no matter how greatly the dogs may need food or water. Cannon and Washburn have published the latest and most convincing work on this subject, and give the literature. They first draw the distinction between appetite and hunger. The former is a mere expectation of pleasure from the taste of food, and may be present when one is not hungry, *e.g.*, in eating candy or dessert. The latter is a dull ache or gnawing sensation referred to the lower mid-chest region and epigastrium, and it may in starvation prompt to the taking of disgusting food for which there is no appetite. A dog like Hedon's therefore may have appetite but not hunger. Various known facts are marshalled to render improbable the view that hunger is a general sensation — the effect upon the central nervous system of depletion of food-substances in the blood — referred to

a local area. Though of local origin, it is considered improbable that hunger is due to turgescence of gastric glands or sensations of the mucous membrane. On the basis of experiments performed upon themselves, the authors conclude that hunger consists in contractions of the stomach and intestine. Hunger-pangs come and go with the successive waves of contraction. Hunger is normally the signal that the stomach is contracted and ready for action.

Therefore, if hunger is of local and not general origin, the question is of interest why diabetic dogs are so much hungrier than normal dogs. It may perhaps be assumed that the phenomenon of hunger is actually of central nervous origin, and is due either to depletion of circulating or reserve food-stuffs, or to some sort of arrangement whereby the nervous system becomes aware that itself or the body is in need of food. Then, instead of *referring* the sensation of hunger to the abdomen, the nervous system *causes* the sensation of hunger by setting up rhythmic gastro-intestinal contractions. Physiologists might perhaps find means to determine whether the enormous appetite of the diabetic dog is entirely secondary to the impaired nutrition due to loss of sugar, or whether it is to any extent primary. Nervous bulimia independent of diabetes, as in syphilis or diabetes insipidus, is known, and some early diabetics, including some obese ones, show this symptom. In dogs, it may appear as though a diabetic animal is hungrier than a normal animal with simple under-nutrition, and that a stranger with a piece of meat may make the diagnosis; but casual observations cannot decide.

The subject of digestion is closely related. By some, causes of indigestion are sought entirely in the alimentary tube or its ferments, or at any rate no farther away than the liver. In these dogs with diabetes, digestion is not quite normal, because of a considerable diminution of pancreatic juice. Yet one may see occasionally a dog which weighs 5–6 kilos and which eats and digests every day one kilo of meat. The nitrogen loss through the feces is not great; by far the greater part comes through the urine. A non-diabetic dog would never take such a diet; if it were forced down him, he could not digest it; diarrhea and vomiting would be inevitable. Yet the diabetic dog, with intrinsically impaired digestion, a weakened general condition, and frequently a fatty liver, is able to digest what the normal animal cannot digest. Here is seen the importance of the call of the

tissues for food. An intestinal tract, with normal ferments and normal power of secreting food-substances from its lumen into the blood, may fall into difficulties because of stagnation of those substances in the blood, or the refusal of metabolic organs to dispose of them properly; the food may then ferment and damage the intestine. But with a constant tissue-hunger, and a poverty of food-substances in the blood, the flow from the intestine may be correspondingly facilitated. At any rate, under such conditions, a weakened organism with a small fragment of pancreas and a fatty liver is able to perform digestive labor impossible for the normal animal.

In conclusion, there is no evidence that operative injury of certain nerves is the cause of diabetes or the diabetic peculiarities of hunger, thirst and digestion.

B. Clinical.

Records of glycosuria from peripheral nervous disturbance in human patients are exceedingly numerous. The disturbance is of every nature, and the glycosuria is of every degree of intensity and duration.

The fullest statistics, and analysis of the same, concerning postoperative glycosuria in human patients, are presented by Pflüger (5 and 11). In his opinion, all the cases fall into two categories: (1) injuries of the head or other nervous injuries; (2) disturbances of metabolism due to infection. Along with postoperative glycosuria may presumably be classified that which in some instances follows fractures, burns and similar injuries. The very high frequency of glycosuria following fractures is especially insisted upon by Cadéac and Maignon (1). The fullest discussion and review of the literature concerning ephemeral glycosuria following trauma is probably that of Kausch (2*A* and 2*B*). Sometimes the condition takes the form, not of spontaneous, but of easy alimentary glycosuria (essentially the same thing in milder degree). This latter phase is discussed in the paper of Haedke.

In Chapter XII, mention was made of various other clinical conditions in which glycosuria has been reported. Among them are gall-stone colic and sciatica. But in both of these conditions, glycosuria is the exception and not the rule. The glycosuria of gouty attacks may be of nervous or unknown metabolic origin.

In all these cases, it is slightly difficult to be sure whether one is dealing with a simple nervous glycosuria or a mild diabetes; gall-stones may be associated with pancreatic injury, gout and diabetes are notoriously akin, and sciatica and other neuralgias are among the recognized complications of diabetes. A case of Frerichs, cited by Naunyn (p. 88) may stand as a pure example of reflex glycosuria due to sciatic irritation. A shot-wound on the posterior aspect of the thigh resulted in a painful condition like sciatica. The urine contained 1 to 2 per cent dextrose during the painful attacks, but at other times was sugar-free. The painful attacks progressively diminished, and with them the glycosuria. Other interesting cases, in which a transitory glycosuria coincided with sciatic attacks, are reviewed by Lepine [(1), p. 254].

The glycosuria or diabetes sometimes accompanying systemic nervous diseases will be considered under the heading of central causes. Focal lesions of the spinal cord may give rise to glycosuria analogous to that resulting from injury of peripheral nerves. A case of Baum, mentioned by Naunyn (p. 75), is of a child with Pott's disease of the thoracico-lumbar junction. There was acute-angled kyphosis, and an attack suddenly came on, characterized by collapse, polyuria and glycosuria. With orthopedic treatment all the symptoms disappeared. Baum considered the condition due to sudden compression of the semilunar ganglion, but perhaps compression of the spinal cord is an easier and equally satisfactory explanation.

It is the development of diabetes, rather than simple glycosuria, upon which authors have laid greatest stress in connection with peripheral nervous disturbances. Diabetes is a less frequent sequel of peripheral than of central disturbance. Among peripheral lesions of possible etiological importance, those of the abdominal sympathetic are among the rarest reported. The scanty material is reviewed in a few sentences by Naunyn (p. 75–6) and by Lepine [(1), p. 415]. Among these are the report by Hale White concerning four cases of fibrosis of the semilunar ganglion, and of Klebs and Munk, also Cavazzani, concerning lesions of the cœliac plexus. Here should be included also the very rare cases of diabetes in association with adrenal tumors. Naunyn (p. 56) was able to find three such in the literature. The first was a case of atrophy of the left with adenoma of the right adrenal. The second was an acromegalic with hypophyseal tumor and cysts of both adrenals. The third was a case of mammary

carcinoma with metastases in the solar plexus and in both adrenals. Garrod (3) mentions two cases of diabetes with sarcoma of the left adrenal. In all these cases, the sympathetic disturbance is alone the important factor, provided any such factor exists. It must be conceded that no clear evidence exists that disease or injury of the abdominal sympathetic has been the cause of the diabetes which accompanied it.

Arteriosclerosis of the pancreatic vessels has received a certain amount of attention in connection with the etiology of diabetes. Von Noorden [(1), pp. 58, 79, 198] considers that arteriosclerosis is more often the result than the cause of diabetes; but it may sometimes be the agency through which syphilis produces diabetes. Naunyn (p. 104) mentions the *pancreatitis interstitialis angiosclerotica*, with references to the publications of Hoppe-Seyler, Fleiner, Dieckhoff and v. Hansemann. Since then, Bleibtreu has devoted a paper to the relations of arteriosclerosis and fat-necrosis to diabetes. In particular, he describes cases of fat-necrosis without discoverable lesion in the pancreas, and suggests a nervous etiology for the whole.

Lesions of the vagus are somewhat more frequent in association with diabetes, but still are rare. In a case reported by Percy [ref. by Pflüger (1), p. 403] the semilunar ganglion, splanchnic and vagus nerves were all found thickened and of cartilaginous hardness. In the same place, Pflüger also refers to cases of Anger, Henrot and Frerichs, in which diabetes was associated with either tumors or calcified lymph-glands in connection with the vagus. Naunyn (pp. 75–6) cites further similar cases described by Newman, and by Thiroloix; also four cases of Fleury with hypertrophy of the vagus, also one of Reichel with phosphorus-poisoning and hemorrhage into the vagus sheath. Lepine [(1), p. 415] adds cases reported by Düben and by Nyman, of calcified lymph-glands pressing upon one of the vagi. The etiologic status in even the best of these cases may be considered suggested rather than proved.

Texts also mention cases of diabetes following traumatisms of the abdomen, in which presumably the sympathetic, vagus or one of the viscera might be injured.

Other peripheral nerve-troubles which have been reported as followed by diabetes are of the most varied nature. In some instances the diabetes is transient, in others permanent. Kausch (2*B*) has reviewed the interesting literature, and a few cases are

presented by Pflüger [(1), p. 399], chosen by him from Frerich's book. They include the following two.

Man aged 58, with trigeminal neuralgia following a severe eye-operation, and associated general cutaneous hyperæsthesia. Diabetes shortly ensued, with daily passage of 8–10 litres of urine containing 5 per cent sugar. The pulse was also increased to 120 per minute. After a Carlsbad cure and a course of creosote the diabetes permanently disappeared, 8 weeks after its onset. Frerichs saw the patient 8 years thereafter. Repeated tests showed the urine permanently sugar-free, though cutaneous hyperæsthesia persisted.

Another man, aged 52, suffered with double sciatica and simultaneously a glycosuria of 6 per cent, which was reduced to traces by strict diet. The sciatica sometimes intermitted for weeks and months, and during these intermissions the diabetes was also absent. These conditions continued for 3 years, till albuminuria supervened, and after it dropsy.

One of the two cases reported by Abt and Strouse was of a child struck by an automobile, with no obvious injury except an open fracture of the right tibia. There was unconsciousness for thirty minutes, so a direct central nervous injury is possible. The broken bone healed uneventfully; but about seven months after the injury, symptoms of diabetes began. The disease proved permanent; it was severe in the sense of difficulty in obtaining sugar-freedom on restricted diet, but the general well-being was maintained better than usual.

May's case of mild diabetes combined with levulosuria, mentioned in Chapter VIII, was one of transverse myelitis.

Naunyn (p. 75) cites a case observed by Smith, of diabetes mellitus associated with a tumor compressing the spinal cord in the mid-cervical region.

Reports of diabetes following upon syphilitic changes in the spinal cord and peripheral nerves are frequent, but the general effects of syphilis are so obscure that the cases can seldom be used to illustrate the present subject.

In conclusion, three remarks are proper concerning the general subject of the association of diabetes with peripheral nervous disturbances.

1. Peripheral nervous lesions as an etiologic factor in certain cases of human diabetes are strongly suggested but not proved.

2. There is room for difference of opinion as to how far the nervous lesion may be the sole cause or merely an exciting cause, and as to the part played by predisposition. The dispute is not so serious as might appear. Few authors would deny the rôle of predisposition. On the other hand, none deny that an existing diabetes may be aggravated, and a latent diabetes brought out, by some peripheral nervous disturbance. The question then is merely of the *degree* of influence of the latter. Granted the predisposition, there seems no room for doubt that nervous injury may make a patient actively diabetic some years before he would otherwise have become so. It thus further becomes probable, as Naunyn (p. 94) believes, that nervous injury may produce diabetes in a moderately predisposed individual who otherwise might have passed safely through his whole life without diabetes. On this basis, nervous injury becomes of practical clinical importance in the etiology of diabetes. For experimental purposes, the lesson is to seek to imitate the recognized clinical conditions by making use of predisposed animals, *i.e.*, those in which part of the pancreas has been removed. They are either the only ones, or at least the easiest ones, in which we may hope for success in the production of neurogenic diabetes.

3. As in the production of glycosuria, so also in the production of diabetes, suspicion attaches primarily to irritative and not to paralytic lesions. A possible reason for the failure of many experimenters is thus indicated, for they not only generally worked with the intact pancreas, but they confined their efforts to the simple resection of nerves, i.e., to attempts at paralytic lesions. The mere scarification of the peritoneal coat of the intestine by Pflüger, the attempts at destruction of the duodenal mucosa, and all such experiments, cannot be expected to set up any chronic irritation of the pancreatic nerves. It is in various ways an attractive hypothesis that diabetes (and nephritis?) is an irritative disorder of the abdominal sympathetic; and it is worth the attention of investigators to devise methods for setting up irritative processes of these nerves in partially depancreatized animals, in the hope of producing diabetes thereby. Nevertheless, it is not demonstrated that diabetes is an irritative disorder, and it might be regarded as a paralysis of the internal function of the pancreas, in analogy with muscular paralyses. The experiments with enervation of the pancreas have not excluded this possibility, for two reasons. (a) The experiments have been per-

formed either in animals with intact pancreas or after ligation of the ducts, and diabetes is unlikely in either case. The islet cells are presumably able to functionate to some slight extent without a nerve-supply, and a very slight function will ward off diabetes. (b) More important, the so-called enervation of the pancreas cannot deprive it of nerve-supply. It contains numerous ganglion-cells in its own substance, and after section of the nerves from without, these cells may take over the regulating function, as other peripheral sympathetic stations are known to do under similar conditions. But if the average case of human diabetes is a functional paralysis of the pancreas, this paralysis may very properly be supposed to include those intra-pancreatic ganglion-cells which the surgeon's knife fails to reach except by extirpation of the entire organ.

2. Glycosuria of Central Nervous Origin.

A. Experimental.

This phase of the subject practically begins and ends with the Bernard sugar-puncture and its modifications. Various facts concerning it have been discussed in Chapter XVI, and other details may be added here.

Claude Bernard [(1), p. 398] describes his discovery, that "the puncture of the space comprised between the origin of the pneumogastrics and that of the auditory nerves produces simultaneously an increase in the quantity of the urine and the appearance of sugar in the urine." A puncture higher up produces less urine and less sugar, and albuminuria may appear. When the puncture is a little below the origin of the auditory nerves, there may be polyuria without excretion of sugar or albumin. Beginning page 401, there is a description of the methods of puncture, and the different instruments devised for the purpose. The subject was so thoroughly studied by "the great physiologist," that few essential facts have been added by later investigators. Descriptions and illustrations of methods and instruments may be found in Cyon's "Methodik" and in Burdon Sanderson's "Handbook." Besides rabbits and dogs, piqûre glycosuria has been successfully produced in other laboratory animals, especially cats, birds, frogs and toads.

After a successful puncture, glycosuria and polyuria generally come on within about half an hour, and persist for several hours.

In one exceptional instance, Bernard saw sugar-excretion continue for a week. In richly nourished animals, the glycosuria is regularly high, and may reach 8 per cent. Bernard proved that liver-glycogen is essential for the glycosuria; results are negative after fasting or after ligation of the hepatic vessels. Schiff and others have found that piqûre causes no glycosuria after extirpation of the liver. In Chapter II, the question of the effect of the piqûre upon the postmortem diastase-content of liver and blood was discussed; investigators have found no demonstrable changes.

Bernard demonstrated that glycosuria is produced neither by puncture with a fine needle, nor by a superficial cauterization of the floor of the ventricle. It is necessary to make a penetrating wound large enough to sever a considerable number of fibres in certain tracts underneath the floor of the ventricle. By the fact that glycosuria still results from puncture after the vagi are cut, he proved that these nerves do not carry the impulse. After cutting the splanchnics, however, glycosuria remains absent. This fact has been confirmed by numerous later workers, notably by Eckhard, so that no doubt remains that the splanchnics constitute the path of the stimulus. Splanchnicotomy after glycosuria has begun does not check the glycosuria; evidently the stimulus has set up some process in the liver which continues longer than the stimulus itself. Laffont's claims of cessation of glycosuria after section of nerve-roots are thus either rendered improbable or robbed of significance (see below). By section of the cord at different levels, Bernard undertook to follow the tracts from the medulla into the cord and to determine at what level they left the cord. His rather vague expression has been interpreted to mean that the fibres leave the cord by the first three dorsal roots. Eckhard also performed sections of the cord, but his statements are self-contradictory. Laffont claimed to show not only that evulsion of the first three dorsal roots prevents piqûre-glycosuria, but also that it checks the glycosuria after it has begun. For these reasons, text-books state that the sugar-regulating fibres leave the cord by the upper dorsal roots. Wertheimer and Battez [(1) and especially (4)] have ably reviewed the subject critically and experimentally. They pointed out the obvious mistakes and contradictions in the early literature, and proved conclusively that piqûre-glycosuria occurs in full intensity after section of the first three dorsal root-pairs. The impossibility of any other result was pointed out, since it is firmly established on the one

hand that the fibres concerned traverse the splanchnics, and on the other hand that no fibres from the upper three thoracic roots enter the splanchnics. Extraneous conditions, such as nervous shock from cutting the cord or tearing out nerve-roots, account for the earlier mistakes. But Wertheimer and Battez merely left it to be supposed in general fashion that the sugar-regulating fibres leave the cord by the same paths as the other splanchnic fibres, viz., by the lower thoracic nerve-roots; they did not attempt to determine the level. Hedon (10) points out the desirability of experiments to determine the points of exit of these fibres, especially by first creating the necessary lesion (section of the cord, etc.) and then waiting for the shock to pass off before testing with the piqûre.

The nature of the effect of piqûre, whether paralysis or irritation, was a question which occurred to Bernard; and though at first inclined to the former view, he finally concluded that its action is by irritation. One of the strongest supports of this opinion has heretofore been the claim of Laffont, that tearing out the first three thoracic nerve-roots stops the glycosuria even after it has begun. It has been supposed that a constant stream of irritation passing from the medulla by these roots is thus interrupted. But after showing that Laffont's claim is erroneous, Wertheimer and Battez (4) conclude that we have no information whether the effect of piqûre is irritation or paralysis. Strictly, this statement is true, but still a little of the previous evidence holds good. Pflüger [(1), p. 392] accepted the irritation doctrine on the basis of the following reasons:

(1) The effect of the puncture is transitory, and disappears long before the wounded area can heal. (2) The puncture can be repeated several times in the same animal, with positive result each time. (3) Glycosuria may be caused by irritation but never by paralysis of a nerve such as the vagus. (4) Piqûre produces no glycosuria in anæsthetized animals. It is not true, however, as Pflüger asserts, that these reasons leave "no doubt." We may set down objections to each of the reasons as follows.

(1) It is true that glycosuria ceases before the wound can heal; in fact, histologic examination months afterward shows that the wound of the nervous tissue never heals. But paralysis is generally also present at first, and may be transitory like the glycosuria. Some mechanism of compensation may come into play in one case as in the other. (2) After compensation, a

fresh puncture might work by adding fresh paralysis. But in my experience with dogs, it is not a fact that successive punctures have the same glycosuric effect. My experience, as far as it goes, is that the first puncture produces the greatest glycosuria, and after two or three punctures, later strokes, no matter how accurate, may sometimes be followed by no glycosuria. (3) The analogy with an afferent nerve is obviously not apropos. (4) The negative results of piqûre in deeply anæsthetized animals might possibly be explained as a failure of the mechanism which ordinarily produces sugar when its central control is paralyzed.

It may be concluded that probability favors the view that the effect of piqûre is irritative, but no real proof exists.

Mention has already been made that piqûre-glycosuria is prevented by preliminary starvation (to relative glycogen-freedom), by high section of the spinal cord, by splanchnicotomy, and by removal of the liver or ligation of its vessels. In Chapter III, reference was made to authors who have proved that glycerin prevents this form of glycosuria. Saikowski and Golobin [ref. by Naunyn, p. 67] found that arsenic poisoning likewise prevents the glycosuria. It is not yet known whether the arsenic acts by depleting the liver-glycogen or by some other process. Masing's results suggest the latter. Macleod and Dolly (ref. by Rosenberger, p. 278) found that nicotin in dosage of 0.008 g. per kilo in rabbits has an inhibitory effect upon piqûre glycosuria. Ligation of the bile-duct, which tends to destroy liver-glycogen, has been claimed to prevent piqûre-glycosuria, but the claim is disputed [see Naunyn, p. 67]. Wertheimer and Battez (2 and 3) proved that atropin, a paralysant of (external) secretory nerves, fails to prevent piqûre-glycosuria, and the same was discovered by Lahousse. Eppinger, Falta and Rudinger (1) claim that piqûre fails to produce glycosuria in thyroidectomized animals, but in view of the findings with adrenalin glycosuria, it may be questioned whether piqûre glycosuria is impossible or merely more difficult. Most interesting is the effect of narcotics. Eckhard discovered their inhibiting effects, and any of the drugs causing profound narcosis — chloroform, ether, chloral, opium, paraldehyde etc., — are now known to prevent piqûre-glycosuria. Frogs and toads punctured during narcosis show glycosuria after waking up. The accepted explanation of the inhibition has been that the benumbed nerves cannot transmit the irritation from the center; it is observed that Pflüger's above reason (4) is built

upon this idea. But Starkenstein (3) has shown that though no glycosuria follows piqûre in anæsthetized animals, the characteristic changes in the adrenals occur nevertheless, *i.e.*, the nerves do transmit the stimulus. He therefore concludes that it is the peripheral nervous mechanism which is benumbed by the anæsthetic, so that it fails to respond to the stimulus. He supports this view by experiments showing that adrenalin glycosuria also is prevented by anæsthetics. Starkenstein's findings are interesting not only as a contribution to our knowledge of the effects of piqûre, but also as an example of the ability of anæsthetized neurones to transmit stimuli. They accord with Crile's surgical views. Neubauer (4) has found that the blood-pressure is increased after piqûre, and that anæsthetics oppose the pressor as well as the glycosuric effect. Opium is less effective than chloral hydrate or alcohol.

After the discovery of pancreatic diabetes, one of the first points of interest naturally was to determine the relations between it and piqûre. Hedon (2 and 3) was the first to prove that piqûre produces its characteristic effects in totally depancreatized animals. Kaufmann and others found the same. Chauveau and Kaufmann made the most elaborate studies of supposed relations between the piqûre, various organs, and supposed nerve-centers, and built up a fanciful doctrine comparable to the recent polyglandular hypothesis, except for invoking nerve-centers instead of hormones. A very clear-cut and satisfactory résumé of their work is presented by Hedon (11). It included experiments with the piqûre after (incomplete ?) enervation of liver and pancreas. Their finding that hyperglycemia still results when either of these organs alone is enervated, but is absent when both together are enervated, may be explained as due to some effect of shock. Nobody has yet demonstrated an effect of piqûre upon the pancreas.

Though piqûre-glycosuria is within certain limits dependent upon glycogen-richness of the liver, yet there may be reason to suppose that in some cases the animal excretes more sugar than corresponds to the glycogen of its liver. Such a result might be explained on two grounds. (1) Von Noorden [(3), p. 536] quotes Luchsinger as having proved that the muscles as well as the liver lose glycogen after piqûre. Pflüger [(1), p. 381 ff] convinces himself that the effect of piqûre is solely upon the liver. It is true that the idea of Chauveau and Kaufmann, of a direct nervous influence of the "sugar-center" upon the general tissues, seems

to be ruled out. But it is still unknown whether piqûre may not affect the muscle-glycogen through hormones from the liver or elsewhere. Experiments with ligation or ablation of the liver fail to settle this point, and it comes down to a simple question of glycogen-analysis. (2) The piqûre may possibly give rise to formation of sugar from protein or fat. No such result has been demonstrated. If such a process occurs, the ideal opportunity for its demonstration would seem to be in glycogen-free animals, and these are the very ones which fail to show glycosuria. Nevertheless, it is possible that the process occurs in these animals to some small extent, but that the sugar is used up as fast as formed. Thiroloix (5) reports interesting experiments, in which the entire pancreas of dogs was removed except a few milligrams. Starvation brought an end to the glycosuria in these animals; and then piqûre caused fresh glycosuria. It is reasonable to suppose that these animals possessed less glycogen than normal fasting animals. The result may therefore mean: (*a*) that since carbohydrate is less firmly bound in these than in normal animals, the piqûre more easily sets free the traces that exist; or (*b*) that piqûre causes sugar-formation from fat or protein in fasting animals, but that the normal fasting animals use it up, while the diabetic animals cannot. In totally depancreatized animals, Hedon (2 and 3) proved that not only D but also D/N is increased, and the finding has been confirmed. By one interpretation, this could mean sugar-formation from fat; but the sweeping out of available carbohydrate is a better supported explanation.

Little work has been done in the study of the general metabolism after piqûre. Concerning the gaseous exchange, there seems to be nothing except the statement of Bernard, that rabbits after piqûre excrete as much CO_2 as normal controls, or a little more; and the later work of Lahousse, who claims the opposite, viz., that both the absorbed O_2 and the excreted CO_2 are reduced, and the respiratory quotient at the same time diminished. Bernard's work cannot be considered decisive. Lahousse used short, 10-minute tests of the respiration. In any event, the underlying processes are complex, and Claude Bernard's conclusion that punctured animals retain full power to utilize dextrose is nearer to the truth then Lahousse's conclusion that the glycolytic power is diminished.

The Bernard "sugar-centre" in the medulla remains the standard and most reliable area for producing nervous glycosuria.

Eckhard however extended the area somewhat, by showing that glycosuria may follow injuries of the medulla outside the limits set by Bernard. Bernard also had found no glycosuria from lesions of the cerebellum. Eckhard obtained positive results by injuries of its vermis. In particular, damage to the most posterior of the convolutions of the middle lobe as seen from above was followed so regularly by polyuria and glycosuria, that he gave to it the name of *lobus hydruricus et diabeticus*. His experiments were chiefly on rabbits. In the higher regions of their brains, particularly in the temporal region, he was able to produce injuries resulting in polyuria and sometimes glycosuria. Ignorance is still very great, however, concerning higher centres governing the sugar-economy. Claude Bernard produced transient glycosuria in a dog by blows on the head; the clinical traumatic glycosuria is thus imitated.

B. Clinical.

The fullest treatment of the subject of nervous diseases associated with diabetes is found in the texts of Naunyn, Lepine, and Rosenberger. We may divide such diseased conditions into (I) *general* and (II) *local*, while reserving (III) *traumatic* lesions as a separate topic.

I. General Nervous Diseases.

These are such as afford no evidence of a localized effect upon any particular "centre." Syphilitic and para-syphilitic diseases (tabes and paralytic dementia) are among the list. The importance of syphilis in the etiology of diabetes is well known but not explained. No hypothesis is more plausible than that its influence is through the nervous system. Multiple sclerosis, epilepsy and other diseases are likewise in this list. In all, the glycosuria may vary in intensity and duration; some cases may be obviously simple glycosuria, others obviously diabetes, and others again hard to classify, especially those of slight chronic glycosuria very little influenced by changes of diet. Meningitis of any type may also be associated with sugar-excretion, and here it is generally a simple glycosuria. Garrod (2) calls attention especially to the glycosuria accompanying tubercular meningitis. In his experience it is present in more than 30 per cent of the cases, but generally only during the last few days of life.

II. Localized Diseased Conditions.

Among localized nervous disturbances giving rise to glycosuria or diabetes, those in the neighborhood of the "sugar-centre" of the medulla are fewest. Lepine [(1), p. 404 ff] presents a series of such. But he properly remarks (p. 408) that glycosuria is the exception and not the rule in such conditions. Great attention has naturally been paid to the few cases in which cysticerci in the fourth ventricle have been associated with glycosuria; but in the majority of cases of cysterci in this location, glycosuria has been absent. Michael has reported the only known case of severe diabetes with cysticercus of this ventricle; death occurred in coma. Hemorrhage into the fourth ventricle sometimes causes glycosuria, but hemorrhage here is rare except from traumatism. The majority of tumors of the medulla do not give rise to glycosuria. Lepine explains this fact on the basis that glycosuria is of irritative not paralytic origin, and accordingly slow-growing tumors fail to set up sufficient irritation. On the other hand, the texts contain several reports of tubercles irritating the medulla and giving rise even to intense glycosuria [6 per cent in the case of Lepine (1), p. 409].

The literature of hemorrhage and tumors of the pons and cerebellum is reviewed by Naunyn (pp. 69 and 70). They may be accompanied either by simple glycosuria or by true diabetes. Lepine [(1), p. 410] describes several cases of glycosuria in association with cyst, tubercle, or focal softening in the cerebellum.

Tumors of the cerebrum may be accompanied by either simple glycosuria or true diabetes. The same is true of foci of softening, also of inflammatory conditions. The most striking instances however are those of apoplexy, for here the suddenness and definiteness of the attack are comparable to the conditions of simple trauma, and it becomes possible to say with strong probability that the nervous injury is the cause of the glycosuria or diabetes. Naunyn (p. 70) states that he knows of only one positive case in which apoplectic glycosuria passed over into true diabetes.

III. Traumatic Lesions.

No one doubts the frequency of transitory glycosuria following trauma of the central nervous system, or that the nervous disturbance is the cause of the glycosuria. But diabetes as a result of nervous injury is a more disputed point.

The injury which gives rise to glycosuria or diabetes involves the head more frequently than any other part of the body. In numerous other cases, the injury is a fall in which the patient alights on his feet, or in some other manner whereby an injury of the head is presumable. In other instances, the injury may be of a general nature, and the central nervous system is perhaps somehow affected by the general shock. Lepine [(1), p. 417] quotes from Jodry the following figures concerning the site of injury in 145 cases of this character:

Head	72 cases or 50 per cent.
Vertebral column	27 cases or 20 per cent.
Abdomen	12 cases or 8 per cent.

In 5 per cent of the cases, the patient fell and alighted on his feet; and in 17 per cent the site of injury was not clearly indicated.

The 72 cases of cranial injury involved the different regions as follows:

Occipital	15 times or 20 per cent.
Frontal	12 times or 16 per cent.
Parietal	12 times or 16 per cent.
Vertex	6 times or 8 per cent.
Undetermined	27 times or 37 per cent.

Lepine, in an analysis of 34 cases, found the time of onset of glycosuria to be as follows:

Within the first 3 days	10 cases.
Within the first week	5 cases.
Within three months	12 cases.
Later	7 cases.

That true diabetes has followed trauma is not denied. The question is only whether the trauma caused the diabetes. Naunyn and Lepine believe unreservedly that such an etiology is possible. Kausch has taken a skeptical attitude, and demands formal proof that a patient's sugar-tolerance was normal before the accident. Von Noorden is also somewhat skeptical. But the question is not merely a theoretical abstraction; it is obviously sometimes of the highest medico-legal importance. Von Noorden [(1), p. 71] therefore lays down the following principles as representing the present state of our knowledge.

(*a*) Traumatic diabetes is to be diagnosed with *positiveness:*

1. If the urine has been proved sugar-free any time within a year before the accident, and is found to contain sugar any time within a year after the accident.

2. If the patient, without urinalysis, was apparently healthy up to the time of the accident, but within a few weeks thereafter showed any of the typical accompaniments of diabetes (weakness, loss of weight, neuralgia, visual disturbance, impotence, thirst, etc.). The urine examination may happen to be delayed indefinitely. But if, under the above conditions, glycosuria is discovered months or even years after the accident, the decision is still positive.

(*b*) Traumatic diabetes is to be considered *possible*, if an apparently healthy person meets with an accident, and begins to show diabetes within one or two years thereafter. Such a diagnosis only becomes *probable*, however, if the injury involved an intracranial lesion or a concussion of the brain, or if a severe traumatic neurosis developed.

The above *practical* and *legal* evidence is emphasized as being distinct from strict scientific proof, such as required for the theory of the subject.

A number of cases of traumatic glycosuria give every indication of being true diabetes, yet recover. As we learn to apply more accurate and positive tests for diabetes, these cases will probably prove to be genuine diabetes, which disappears as its cause is removed. Other cases persist, are severe in nature and rapid in course. It is possible that a diabetes may persist after its original cause is removed; if the action of the cause is too intense or prolonged, removal of the cause may then not be enough to check the disease. As to the part played by trauma, we may apply the same reasoning concerning central as concerning peripheral injuries. Trauma can at least aggravate an existing diabetes, and bring out a latent diabetes. It may presumably make a person diabetic who otherwise would have lived to die of something else. The question is then merely of degree, to what extent the patient's condition is due to the nervous lesion and to what extent to an unknown predisposition. Leaving aside indefinite cases, we may find it possible to distinguish two extremes, according as the traumatic diabetes is due preëminently to trauma or preëminently to predisposition.

First, there is a group of cases in which I believe it possible to consider the nervous injury the actual and sole cause of the

diabetes; the injury sets up in these patients the nervous condition which develops spontaneously in other patients, and of which the manifestation is diabetes mellitus. When we read the reports of apparently healthy persons, in whom a serious nerve-lesion is followed promptly by diabetes, we are likely to gain the impression that to imagine a preëxisting latent diabetes in all these persons is rather far-fetched. Cases of this nature are described in the texts.

One of the two cases in children, reported recently by Abt and Strouse, has been already mentioned. The other was a boy of thirteen, who fell from a second-story window, landing on his head. Symptoms of diabetes promptly developed and rapidly increased, so that the disease was found to be severe, when the patient was seen, three months after the accident. The only feature suggestive of predisposition in either child was that both were Jewish.

One of the most convincing examples has lately been reported by Weiland. His patient was a farm-laborer of healthy family, free from diabetes, obesity, gout, and nerve- or lung-troubles. The patient's own history was negative except for several colds, and sciatica once. A physician testified that he had known him for years past, and that his urine was constantly free from sugar. While he was digging a well, an empty bucket fell from a height of about 8 metres and struck him on the back of the head. He was unconscious for half an hour, but suffered no bleeding from nose or ears, or loss of memory. On regaining consciousness, he was able to walk home. The wound of the soft tissues was sutured by his physician, and healed perfectly. Within a week after the accident there began marked weakness, thirst, frequent micturition and pruritus. The first urine test was made fifteen days after the accident, and showed sugar. In the clinic, on mixed diet, the urine was normal in quantity but contained 4.7 per cent dextrose. Dieting stopped the glycosuria promptly and developed a certain tolerance of bread. No organic changes were discoverable in the body or nervous system. The patient was dismissed with rules for his diet, under a physician's observation. A little over a year later he was again examined at the clinic, and a downward course of the disease was evident as respects quantity of urine, bread-tolerance, and general symptoms. Weiland concludes that this patient follows the usual law concerning such cases, "that traumatic diabetes, which in occasional cases may

recover, as a rule irresistibly grows worse, and leads to death within a period of three months to five years." Weiland's opinion is that such a patient, apparently free from hereditary or personal taint, gives the impression that trauma alone can suffice to produce diabetes in absence of predispostion.

Second, there is another group of traumatic diabetes in which predisposition is almost everything and trauma almost nothing. Such cases are described by Naunyn (p. 82). One is of a man aged 40, with mother and brother nervous and cousin epileptic. According to his physician, his urine was sugar-free. In the dark he stumbled over a pile of stones without injuring himself. However, weakness, anxious feeling, dizziness and general unwellness followed; sugar was found in the urine, and a mild diabetes persisted. In another instance, a railway employee fell about 1 metre, in a standing position, alighting upon his feet and apparently unhurt except for a pain in his right hip. Traumatic neurosis and mild diabetes were the result.

A predisposed nervous system may fairly be supposed in cases of this sort. The trauma presumably acts only as a slight exciting cause. Such cases serve as a connecting link between glycosuria or diabetes from physical shock, which we have been considering, and those from psychic influence, which constitute the next topic. Naunyn (p. 94) calls attention to the special effectiveness of the combination of the two, viz., of circumstances in which physical and psychic strain or shock are combined. As a piece of the strongest evidence in favor of the influence of the nervous system in the etiology of diabetes, he quotes figures showing that locomotive engineers die twice as frequently of diabetes as those in other occupations, and statistics of a French railway showing seven times as much diabetes among the engineers as among the other employees of the line. The statistics are quoted by Lepine [(1), p. 424] in greater detail as follows: Cases of diabetes per thousand among, —

Engineers and firemen	12.6
Conductors and brakemen	13.1
All other employees	1.75

The preponderance among the classes exposed to physical [vibration a factor?] and psychic stress seems evident.

In review of this topic, we may conclude that the status of central nervous injuries as the sole or contributing cause of dia-

betes in certain cases is established by as perfect evidence as the clinic ordinarily affords. No nervous factor in the production of diabetes has ever been demonstrated experimentally. The general lesson which the laboratory may learn from the clinic is that central are apparently more effective than peripheral nervous lesions, that the effective disturbance is apparently irritative rather than paralytic, and that predisposition greatly increases the chance of the production of diabetes by nervous injury. In partially depancreatized animals we have the predisposition; in the Bernard puncture we have presumably an irritative lesion; and there is anatomical basis for the belief that such a lesion may have an influence upon the pancreas through its sympathetic nervous supply.

3. Glycosuria of Psychic Origin.

A. Experimental.

The first discovery of glycosuria of psychic origin in experimental animals was made by Boehm and Hoffmann (2 and 3). Since they were able to produce it by merely tying cats on the operating table, they gave the condition the name of "Fesselungsdiabetes." Glycosuria begins in perhaps half an hour, and lasts several, even as long as 13, hours. In some cases polyuria accompanies the glycosuria, in other cases the urine is not increased. Hyperglycemia is present; but in the hours preceding death, glycosuria may cease while hyperglycemia persists, and considerable sugar-free urine may be passed during this period. Dextrose or glycogen injected intravenously was utilized, even up to death. In the production of glycosuria the factors of cooling, pain, and circulatory disturbance were considered and evaluated by the authors. It is desirable to keep these factors separate. So far as cold, or organic circulatory or nervous disturbance have a part in this glycosuria, they have their distinct classification elsewhere. If the condition in Boehm and Hoffmann's cats is to be considered as a distinct entity and as composed of several of these factors, the name of "Fesselungsglykosurie" may be retained. If the experiments are planned so as to eliminate all but the psychic disturbance caused by tying, then "binding-glycosuria" may be named as a subdivision under emotional glycosuria. But it is principally essential that we should have a name which includes all forms of glycosuria due to psychic

disturbance, and the standard term for this general condition should therefore be *emotional glycosuria.*

Other animals may occasionally show glycosuria of psychic origin. Rabbits are rather notorious for excreting traces of sugar after almost any sort of manipulation; but the phenomenon is not constant. Cannon, Shohl and Wright refer to Fischer's statement that he has bound rabbits for as long as 24–36 hours on a holder, without finding glycosuria; they explain it by the fact that rabbits often appear stupefied rather than excited by such treatment. Gib (ref. by Kleen, p. 37) "has recently given the account of a bitch that always objected strongly to being shut up, and was greatly agitated during her seclusion, and that constantly after such treatment, but never otherwise, presented small quantities of glucose (up to 0.55 per cent) in the urine." Rosenberger cites similar examples. Velisch (ref. by Kleen, p. 38) has reported glycosuria in the frog from tying it on its back, or from standing it on its head in a narrow cylinder. The latter result has been objected to on the ground of asphyxia. The raging of certain wild species when caged would afford an excellent opportunity of looking for emotional glycosuria, but no observations are reported. In general, the cat remains the animal *par excellence* for the production of emotional glycosuria; no other species is known to show it so regularly and intensely. In normal dogs the glycosuria is absent, though Gigon (2) refers to hyperglycemia in them under these conditions.

The latest work on this subject is by Cannon, Shohl and Wright, who produced glycosuria on a purely emotional basis, by keeping their cats free from all pain or discomfort except the anger at being tied. Glycosuria was found to vary with the psychic state, the animals showing the greatest rage also excreting the most sugar. Three of them, which were quiet when tied and accordingly excreted no sugar, showed glycosuria when confined in a cage near to a dog which barked at them. It was found that epinephrectomy prevents emotional glycosuria, though the cats may show anger as before. Cannon and de la Paz stated that emotion causes an increase of adrenalin in the blood of cats.

No diabetes has ever been produced by psychic influence in experimental animals. That emotional glycosuria is not diabetes is proved by the early onset (sooner than after total pancreatectomy), and by the observation of Boehm and Hoffmann that tied cats are well able to utilize injected dextrose even up to the time of death.

B. Clinical.

Glycosuria is admittedly frequent among the insane. Dawson's paper suggests relations between them. Toy [ref. by Lepine (1), p. 257] has observed transitory glycosuria especially among melancholics, and, in general, in depressive conditions. Sometimes the glycosuria coincided with a recrudescence of delirium. Schulze [ref. by Cannon, Shohl and Wright] reported that the degree of glycosuria is dependent on the degree of depression, and that the greatest excretion of sugar occurs in the fear-psychoses. Oppler mentions the frequent reports of this nature, which were only partially confirmed by Ehrenberg (Monatsschr. f. Psychiatr. u. Neurol., 25, Heft 1) and Tintemann (Monatsschr. f. Psychiatr. u. Neurol., 29, 294); while on the other hand Knauer and Schulz (Allgem. Ztschr. f. Psychiatrie 66, Heft 5) demonstrated glycosuria in a very large number of cases of psychic disorder. In traumatic neurosis and other neuroses, either spontaneous glycosuria or easy alimentary glycosuria is frequent. But there appears to be an absence of relation between hysteria and either glycosuria or diabetes.

The importance of functional states of the nervous system in the etiology of diabetes is difficult to estimate. Diabetes is recognized as developing frequently on a neuropathic basis. Diabetes and insanity may be associated in the same individual or in the same family. Apparently a person predisposed to one is not infrequently predisposed also to the other. The very frequency of this association is however a further indication that diabetes mellitus is a disease of the nervous system.

Diabetes consequent upon mental shock in the non-insane is not infrequently reported. Simple glycosuria is less often mentioned, probably because the urine is seldom examined unless some associated symptom gives an indication. When the condition is evidently diabetic, it may still be transitory, as seen in the following case quoted by Naunyn (p. 82) from Gros. A physician aged 28 suffered from attacks of migraine, and after worry in his practice showed diabetes, with debility and a glycosuria of 6 per cent. On dietetic treatment the sugar disappeared and the strength returned, while the migraine attacks continued. Polyuria occurred with each attack, and this "urina spastica" contained 2–3 per cent sugar, while otherwise the urine was sugar-free. This case suggests not only an influence of worry, but also

the general relations between diabetes and the nervous system. Naunyn (p. 91) also quotes a case from Frerichs, of a man who became diabetic upon finding his wife guilty of adultery; and recites two cases in his own practice. These were in women, one of whom developed diabetes during the bombardment of Strassburg, and the other in consequence of being frightened by a suicide in the same house.

Lepine [(1), p. 424 ff] describes similar cases. An engineer in a train-wreck suffered no injury, but felt severe mental shock, and trembled for 24 hours. Intense thirst began a few minutes after the accident, and sugar was found in the urine. Another engineer of a wrecked train suffered only the psychic shock. During the following days, thirst, weakness and glycosuria appeared. Lepine considers this a case of latent preëxisting diabetes. In another instance, a woman saw her nephew suffer a fall, and developed a state of chronic anxiety. Four weeks later, polydipsia, polyuria and glycosuria were observed, and death ensued from severe diabetes in 17 months. Small hemorrhages in the floor of the fourth ventricle were found at autopsy. Another case is of a tailor, who sustained three different intense emotional shocks within eight hours. Less than two months later, thirst and polyuria were complained of, and within five months he died in coma. The pancreas showed a slight periacinar but no intraacinar fibrosis. In these two last cases, it will be noted that anatomic findings throw some doubt upon the precise rôle of the emotional shock.

There is no case anywhere in the literature which permits judgment as to what part of the effect is due to psychic influence and what part to predisposition. All authors admit the unmistakeable effect of emotion in aggravating an existing diabetes. Naunyn (p. 91) quotes from Teschemacher the case of a diabetic child, sugar-free, which after being frightened by a dog jumping at it immediately showed a glycosuria of 3 per cent; also from Lorand the case of a man under diabetic treatment with glycosuria of only 0.3 per cent, who received the news of a heavy property-loss, and on the next day excreted 5 per cent sugar, under conditions otherwise unchanged. Not only is an open diabetes aggravated, but a latent diabetes is undoubtedly made active by psychic shock, and therefore such shock is at least an exciting cause of diabetes. Worry, anxiety, nervous strain are among the most frequent events in the diabetic anamnesis. The nervous,

mentally active races, and classes of society, are those in which the incidence of diabetes is by far the highest. Lepine [(1), p. 426] states his belief that the psychic are more important than the traumatic causes of diabetes. It is readily understood how an organic nervous lesion, by injuring the nerves or centres governing the pancreas, might constitute an actual cause of diabetes; but it might be questioned how an emotional shock could serve as anything more than the exciting cause. But since diabetes is presumably in most cases a functional disease of the nervous system, the possibility exists that a sufficiently intense functional influence may give rise to the disease. It is doubtful if this result can ever happen in an absolutely normal individual, just as it can never be obtained in any normal laboratory animal. The predisposition, when present, is perhaps in some cases so slight that without the psychic shock the person would never have developed diabetes. In a large proportion of cases however the predisposition is certainly the most important element in the production of the disease.

The clinic therefore proves definitely that emotional stress acts at least as an exciting cause and an aggravating influence in diabetes. The emotional states which produce these results are the ones which in laboratory animals are proved to be associated with stimulation of the abdominal sympathetic. This evidence therefore agrees with that offered by peripheral and central organic nervous lesions, that the processes which make for diabetes are irritative and not paralytic in nature. Predisposition is important. Laboratory attempts should therefore be made with predisposed animals, and with emotional states which excite the abdominal sympathetic.

Experiments.

The experimental material will be presented in the same order as heretofore followed in this chapter, viz., (A) Peripheral, (B) Central, (C) Emotional.

A. Peripheral.

These experiments were performed with animals predisposed to diabetes by removal of a considerable portion of the pancreas. The peripheral nervous lesions consisted in those classes of injuries to which authors have attributed more or less importance in connection with diabetes.

Dog 112; male; age 6 months; weight 7380 g.

Removal of pancreatic tissue weighing 16.7 g. Remnant about lesser duct estimated at 1.5 g. Remnant dissected entirely free from everything except the naked duct and blood-vessels. Diabetes. Death from peritonitis.

Dog 66; female; age 3 years; weight 13 kilos.

Removal of pancreatic tissue weighing 27 g. Remnant about main duct estimated at 2.7 g., and about lesser duct a remnant estimated at 0.25 g. Duodenum and pancreas-remnant sutured to parietal peritoneum, bringing pancreas-remnant close against parietal wound. Diabetes gravis.

Dog 84; male; adult; weight 7 kilos.

Removal of pancreatic tissue weighing 13.3 g. Remnant about main duct estimated at 1.3 g. Duct encircled loosely with loop of wire, not constricting it. Diabetes gravis.

The above three experiments show that when the usual proportion of pancreatic tissue is removed, diabetes is not *prevented* by as complete as possible "enervation" of the pancreas, by suturing it into an abnormal position, nor by a foreign body about the duct.

Dog 53; male; age one year; weight 8300 g.

Removal of pancreatic tissue weighing 17 g. Remnant estimated at 2 g. left about lesser duct, and another estimated at 3 g. left about main duct. Both were "enervated" as completely as possible; also, the principal vessels to the main remnant were ligated, in the hope that some small collateral branches might suffice for nutrition.

Death occurred 3 days after operation, from peritonitis, of which necrosis of the larger remnant was the cause. Urine sugar-free throughout.

Dog 141; male; age 1 year; weight 10,550 g.

Removal of pancreatic tissue weighing 22.9 g. Remnant about smaller duct estimated at 3.1 g. The vessels and nerves supplying the remnant from below were completely blocked by double ligatures; those from above were left free. Though the remnant was $\frac{1}{8}$–$\frac{1}{9}$ of the pancreas, a size which sometimes permits diabetes levis, this dog was sugar-free on bread diet. The ligatures therefore were without diabetogenic effect.

Dog 143; male; age 1½ years; weight 13,350 g.

Removal of pancreatic tissue weighing 23.2 g. Remnant communicating with both ducts estimated at 3.7 to 4 g. Its vessels and nerves from below were ligated, and the margin of the remnant farthest from the duodenum was trimmed. There was as usual no post-operative glycosuria, and the subsequent condition was a very mild transitory diabetes levis, which occurs sometimes with this size of remnant (about $\frac{1}{7}$ of pancreas) when ligatures and trauma are avoided.

Dog 150; male; age 5 years; weight 9900 g.

Removal of pancreatic tissue weighing 17.9 g. Remnant about main duct estimated at 2.2 g. A ligature was placed so as to pucker the mesentery about the lower end of the pancreas remnant, thus compressing it. Diabetes gravis did not result. The dog died of unknown cause before tests for diabetes levis were made. The pancreas-remnant was healthy at autopsy.

The following three animals belong in series.

Dog 153; male; age 4 years; weight 12,300 g.

Removal of pancreatic tissue weighing 24.3 g. Remnant about main duct estimated at 3.4 g. ($\frac{1}{8}$–$\frac{1}{9}$ of pancreas). Diabetes gravis.

Dog 162; male; age 3 years; weight 8100 g.

Removal of pancreatic tissue weighing 15.2 g. Remnant about main duct estimated at 3.9 g. (about $\frac{1}{5}$). No diabetes.

Dog 164; female; age 5 years; weight 9750 g.

Removal of pancreatic tissue weighing 16.3 g. Remnant about main duct estimated at 4 g. (about $\frac{1}{5}$). No diabetes.

The special feature in the above three operations was that the remnant in each case was not "enervated," but was dissected entirely free and all the small vessels and nerves destroyed, except about the duct, where the principal bundle of vessels and nerves entered. Diabetes resulted in the first case with a remnant a trifle larger than the average; in the latter two animals, larger remnants prevented diabetes as usual. No effect of the special trauma is demonstrable.

Dog 67; female; age 4 years; weight 14,500 g.

Removal of pancreatic tissue weighing 17.5 g. Remnant estimated at 3.6 g. (about $\frac{1}{6}$). The remnant was trimmed along the margin, so as to consist of a long narrow strip communicating with both ducts. The nerves found were not cut, but were roughly stripped out by blunt dissection. No post-operative glycosuria; no diabetes; considerable sugar-tolerance as tested by glucose-feeding.

Dog 152; male; age 2 years; weight 13,360 g.

Removal of pancreatic tissue weighing 27.7 g. Remnant about main duct estimated at 4.4 g. ($\frac{1}{7}$–$\frac{1}{8}$). The remnant was rather long, and was brought down to this size by pinching off the edge with the fingers. Vessels and nerve-trunks were left uninjured. The first urine after operation contained 1.2 per cent sugar, which promptly disappeared. The later condition was diabetes levis. Therefore, no effect of the trauma except the unusual occurrence of post-operative glycosuria.

Dog 174; male; age 4 years; weight 12,300 g.

Removal of pancreatic tissue weighing 22.3 g. Remnant about main duct estimated at 3.4 g. ($\frac{1}{7}$–$\frac{1}{8}$). Pancreas bloody; many ligatures necessary; intentional roughness of dissection; and the lower end of remnant was intentionally lacerated. Main vessels and nerves left intact. Doubtful trace of sugar in post-operative urine. No diabetes; lived on bread without glycosuria.

Dog 82; male; weight 12,170 g.

Removal of pancreatic tissue weighing 18.1 g. Portion left about main duct estimated roughly at 5 g. A bloody and difficult pancreas. A double silk ligature was passed loosely about main duct, and a rubber catheter was anchored by sutures to the pancreas and brought out through the wound as a drain. The dog recovered, but chewed off the catheter. Fifteen days after operation, a second operation was performed; the remaining short piece of catheter was found in an abscess bordering the pancreas; the dog died. He had held weight on bread diet, and there was no trace of glycosuria at any time.

Dog 179; age 3 years; weight 9900 g.

Removal of pancreatic tissue weighing 18.5 g. Remnant about main duct estimated at 2 g. ($\frac{1}{10}$–$\frac{1}{11}$). Pancreas bloody;

numerous ligatures and considerable traumatism involved in the operation; main vessels and nerves all spared. Death three days later from peritonitis. The course of the glycosuria was precisely as in absence of infection; *i.e.*, no post-operative glycosuria, but on the day before death, onset of glycosuria of 3.8 per cent.

In Dog 82, infection did not cause diabetes. In Dog 179, it did not prevent diabetes. A series of other records were presented in Chapter X, showing that, contrary to Pflüger's belief, neither general nor local peritoneal infection has any specific influence in connection with diabetes.

Dog 146; female; very old; weight 11,540 g.

Removal of pancreatic tissue weighing 22.8 g. Remnant with edge pinched off, supposedly communicating with both ducts, estimated at 2.8 g. (about $\frac{1}{9}$). The edge of the remnant was pinched off to reduce it to this size. The principal blood-vessels were saved, and the remnant was not completely "enervated"; but at 5 places, the principal nerves found entering it were picked up and broken by stretching. The usual absence of post-operative glycosuria; diabetes gravis began on third day after operation. The example shows that traumatism of this sort does not *prevent* diabetes.

Dog 133; male; age 1 year; weight 9020 g.

Removal of pancreatic tissue weighing 16.4 g. Remnant about lesser duct estimated at 1.6 g. (about $\frac{1}{11}$). Nerves broken as in Dog 146; important vessels injured in the process, and ligated. Death 3 days after operation from necrosis of remnant. No glycosuria.

Dog 139; female; age 3 or 4 years; weight 14,960 g.

Removal of pancreatic tissue weighing 17.6 g. Remnant about main duct, possibly communicating with smaller duct, estimated at 3 g. (about $\frac{1}{7}$). Operation and result as in the previous dog.

Dogs 133 and 139 are analogous to human patients with acute necrosis of the pancreas. In such patients, glycosuria is slight or absent [Opie, Coenen, and other literature]. Likewise in these dogs, though the pancreas-remnant may be small enough to permit diabetes, and though it may undergo complete destruction, the general intoxication and weakness prevent glycosuria.

Dog 135; male; age 2 years; weight 6730 g.

Removal of pancreatic tissue weighing 16.6 g. Remnant about smaller duct estimated at 3 g. ($\frac{1}{6}$–$\frac{1}{7}$). Considerable dissection was done about the remnant, and most of the small vessels and nerves broken. Dissection was also done in the portal fissure, and a few fibers of the hepatic plexus broken. No glycosuria or diabetes.

Dog 145; male; age 1 year; weight 10,000 g.

Removal of pancreatic tissue weighing 21 g. A remnant was left between the two ducts, communicating with both. By pinching off the margin the weight was brought down to 3.5 g. by estimate ($\frac{1}{7}$). All blood-vessels were saved, but the important nerves were broken with forceps at 5 places (above, below, and opposite remnant). No post-operative glycosuria. Diabetes levis.

The above two animals show that dissection and nerve-injuries about the remnant render an animal neither more nor less liable to diabetes. The size of the remnant is alone essential. The series up to this point has also served to demonstrate the negative effects of various injuries and irritations. In the following animals, the procedure was adopted of avoiding trauma as far as possible in the primary operation, then, after the animal's condition had been observed, performing a secondary operation for the sake of trauma.

Dog 148; male; age 1 year; weight 14,500 g.

Nov. 16, removal of pancreatic tissue weighing 26.7 g. Remnant about main duct estimated at 3.3 g. (about $\frac{1}{9}$). The original operation was conducted as carefully as possible, to avoid any injuries to vessels or nerves that might tend to diabetes. Transient diabetes gravis resulted (with permanent polyuria and diabetes levis). On December 4, all the nerves that could be found along the main vessels to the remnant were dissected out and broken, and one large vein was ligated. There was the merest trace of post-operative glycosuria, and no effect upon the diabetes.

Dog 154 (see protocol); male; weight 14,360 g.

November 24, removal of pancreatic tissue weighing 23 g. Remnant about main duct estimated at 5 g. ($\frac{1}{4}$–$\frac{1}{5}$). At the original operation, the remnant was partially bisected by a temporary ligature. There was no obvious result, though this dog on Decem-

ber 2–5 showed the rare (temporary) condition of glycosuria from excessive meat feeding (like Dog 38). There was also polyuria, but less than in Dog 148, in which no traumatism was done to the remnant.

On December 7, all the vessels (and nerves) were ligated above the remnant, and all the nerves accompanying the vessels from below were dissected out and broken. There was not even a post-operative glycosuria, and 250 cc. milk or 1500 g. meat could be eaten without excretion of sugar.

Dog 93; male; adult; weight 8400 g.

September 21, removal of pancreatic tissue weighing 21.2 g. A few tiny shreds left along vessels, and a remnant communicating with the lesser duct, total weight estimated at 2.6 g. (about $\frac{1}{9}$). No glycosuria or diabetes. On October 9, the omental covering was stripped from the remnant, and it was sponged roughly with gauze, so as to leave its entire surface abraded and oozing. After the operation, the dog received glucose solution instead of water to drink, in order to assist toward diabetes if possible. There was not even a post-operative glycosuria. It was desired to keep the animal for another operation, viz., to prove that the actual removal of a very small piece of pancreas-tissue would bring on diabetes. This is a fact, but death from distemper prevented its demonstration in this dog.

Dog 97; female; age 11 months; weight 12,000 g.

September 27, removal of pancreatic tissue weighing 26.9 g. Remnant about lesser duct estimated at 2.6 g. ($\frac{1}{11}$—$\frac{1}{12}$). Diabetes gravis remained absent because of accidental injury which blocked the duct. The condition was a mild diabetes levis. On November 6, the dog was glycosuric by reason of the diet, and an operation on the pancreas-remnant was performed. This was found as a small atrophic nodule, and was dissected entirely free except for its vessels, being thus "enervated" completely. There was not even a continuance of the former glycosuria; the starvation caused it to cease as promptly as if there has been no operation.

Dog 74; male; adult; weight 6670 g.

August 19, removal of pancreas except portion surrounding main duct. Part removed weighed 11.5 g. Part left estimated at 2.3 g. ($\frac{1}{6}$). A heavy ligature was passed loosely about the

duct, not constricting it; and the duodenum and pancreas remnant were anchored by sutures close to the parietal wound. No diabetes. By October 20, polyuria had developed. On this date, the remnant was dissected entirely free from the duodenum, except for pedicles consisting of duct, vessels and nerves. There was no attempt to "enervate," the purpose being to test the effects of such an operation with nerves intact. Afterward, glucose solution was given instead of water to drink, and glucose was mixed with the feed. It was possible thus to produce glycosuria, just as before the operation. The dissection about the remnant was without diabetogenic effect.

Dog 161; female; age 2 years; weight 7470 g.

November 29, removal of pancreatic tissue weighing 11 g. Remnant about main duct estimated at 0.6 g.; processus uncinatus transplanted subcutaneously estimated at 1.4 g. Both remnants "enervated" as completely as possible. The remnant bordering the duodenum was less than one-twentieth of the pancreas, but the subcutaneous graft amounted to one-ninth of the pancreas, so the total fraction possessed by the animal was between a sixth and a seventh. Diabetes levis resulted, as was to be expected; so no result from the breaking of nerves is perceptible.

On December 21, the subcutaneous graft was dissected free, except for its pedicle. On December 23, the greater portion of the graft was extirpated. There was notable hypertrophy of the graft (weight 6.2 g.), though part of it was inflammatory reaction. The apparent absence of pain in these operations would seem to bear witness to the completeness of the enervation in the original operation. No post-operative glycosuria followed either operation, and the condition (December 27) was still diabetes levis.

On January 4 the duct of the pancreas was divided, with slight trauma to the duodenal remnant. There was not even a post-operative glycosuria.

On January 17, the last of the subcutaneous graft was extirpated. The evening urine of the day of operation was sugar-free. Later (January 22) a transient diabetes gravis ensued, the course of which will be described in a later chapter. The late onset of this diabetes appears to speak against the assumption of some authors, that diabetes following removal of a graft is due to the cutting of the nerves of the pedicle. In this instance it will be remembered that the pedicle had previously been enervated as

completely as possible, by dissecting the vessels entirely naked at two different points along the pedicle. The whole experiment seems to me to afford some testimony in favor of the internal secretory as opposed to the nervous hypothesis.

Dog 89; male; weight 7425 g.

September 17, removal of pancreatic tissue weighing 13.7 g. Remnant about main duct estimated at 1.2 g. (about $\frac{1}{13}$); the end of the processus uncinatus transplanted subcutaneously estimated at an equal size. Aside from glycosuria on September 25 and 29, the dog was sugar-free on bread diet.

On October 4, the subcutaneous graft was removed. The condition was then diabetes levis.

On October 30, the removal of 0.5 g. tissue from the duodenal remnant resulted in the usual absence of post-operative glycosuria; but milk-feeding on November 1 brought out a heavy glycosuria on November 2, and the condition turned out to be true diabetes gravis.

If in the original operation on September 17 no graft had been left, the small size of the duodenal remnant (one-thirteenth of the pancreas) would infallibly have resulted in diabetes gravis. Since the removal of the graft in a secondary operation fails to produce diabetes gravis, it might be supposed that the nervous disturbance attending the single operation has a part in the result, and that the same result fails to follow the secondary removal of the graft because of the slighter nervous shock. Examining the matter more closely, it is seen that both the graft and the duodenal remnant hypertrophied. The tissue removed on October 30 weighed at least 0.5 g. At autopsy, the remnant still present was found to weigh 1.75 g., so that the total weight may be placed at 2.25 g., as compared with the estimate of 1.2 g. for this remnant at the time of the original operation. This weight of 2.25 g. corresponds to nearly one-seventh of the pancreas, hence is of the size which regularly prevents diabetes gravis but permits diabetes levis. The conditions of this experiment are therefore satisfactorily explained on the assumption that the presence of the graft merely afforded time for the pancreas-remnant to hypertrophy. Any difference due to nervous shock is not indicated.

The most important peripheral nervous centres in relation with the pancreas are the semilunar ganglia. Glycosuria has

occasionally been reported from operations upon them, but there is no indication that such glycosuria was of pancreatic origin. I had planned a series of extirpations of these ganglia, but it was interrupted. An attempt to set up an irritative condition in one of these ganglia is represented by the following experiment.

Dog 28; female; age 2 years; weight 7750 g.

April 14, removal of pancreatic tissue weighing 20.3 g. Remnant surrounding both ducts estimated at 4.5 g. ($\frac{1}{5}$–$\frac{1}{6}$). At the same operation, a large Pegenstecher ligature was passed around and partly through the left semilunar ganglion, and its ends left protruding outside the skin. It was hoped in this way to be able to irritate the ganglion by pulling on the ligature, and also that the infectious process following along the ligature might set up a chronic irritation in the ganglion. A subcutaneous injection of 25 g. glucose was also given in the evening of the day of operation. The urine preceding this injection was heavy with sugar, and the specimen of the next morning was still heavier, so that the result was not absolutely negative. The dog's persistent vomiting may also have stood in some connection with the irritation of the ganglion. The experiment was interrupted by the meddling of the dog, which chewed off the protruding portion of the ligature. Therefore on April 24, the buried portion was removed by operation. All this time, the dog was thriving on a diet of bread only, and glycosuria was absent. There was complete final recovery, without diabetes.

In another animal close on the verge of diabetes, an incidental operation was performed on the neck, the only special feature being a considerable irritation of the vagus. In consequence, the postoperative urine contained 1.1 per cent dextrose, but subsequent specimens were negative.

The results of this series are therefore chiefly of negative value. The value of "enervation," nerve-stretching, and various traumatisms in and about the pancreas, for the production of diabetes, seems to be definitely ruled out. The frequent glycosuria reported by other writers after pancreatic operations may have to do with their ligation of the duct; at any rate, in my experience operations involving ligation of the duct have been followed more frequently than others by transient glycosuria. In operations

such as represented in the preceding series, in which the duct is not tampered with, post-operative glycosuria has been a rarity.

The negative results do not mean that this field will prove unproductive. They serve merely to mark off the unproductive portions. I have regretted that I could not proceed along the lines which offer the possibility of something positive. Two such lines seem to be promising.

(1) The effects of chronic irritative lesions of peripheral nerves, imitating recognized clinical conditions, should be tested in partially depancreatized animals. Ligatures about *both* semilunar ganglia, in the manner used for Dog 28, may be of service, or possibly some arrangement of buried electrodes may permit repeated electrical stimulation. Injection of irritant substances, or other devices for chronic irritation, may also be worth trying. Similar attempts are in order in connection with the splanchnic nerves, vagus, and especially the inferior cervical ganglion. Biedl's thoracic-duct glycosuria (which is somehow a nervous glycosuria) should also be tried in animals predisposed by removal of suitable portions of pancreatic tissue.

(2) When all the pancreas is extirpated except a subcutaneous graft, it is possible not only to "enervate" this graft, but also to paint the pedicle with suitable drugs through several hours. By such painting, it should be possible, for example, to make sure that all nerve-impulses are blocked, while the circulation remains. Since diabetes requires only a few hours to develop, it may be feasible, by such methods, to decide whether any nervous impulse to or from the pancreas is essential to the prevention of diabetes.

B. Central.

The central nervous lesion utilized in my experiments has been the piqûre. The first point is to determine whether the condition following piqûre is "diabetes," as it has so often been called. The following are a series of male rabbits in medium nutrition, catheterized at the hours stated. The accuracy of the punctures was confirmed by autopsy.

RABBIT 60; weight 1,970g.

Date	Hour	Treatment	Urine		
			Quant cc.	Sugar	Albumin
May 16	11 A.M.	Piqure.			
	11.30		8	slight	0
	12.20 P.M.		19	mod.	0
	1.30		15	"	0
	3.30		5	"	0
	3.45	Subcut.injection of 20cc. 80% dextrose.			
	5.30		3	"	0
	7.30		3	slight	0
	10.30		1/2	"	0
" 17	9.30 A.M.		30	0	0

RABBIT 61; weight 2,250g.

Date	Hour	Treatment	Urine		
			Quant. cc.	Sugar %	Albumin
May 16	2 P.M.	Piqure.			
	4		15	2.43	0
	5.30		8	2.92	0
	5.45	Subcut.injection of 20cc. 80% Kahlbaum dextrose.			
	7.30		8	3.65	0
	10		2 drops	very heavy	0
" 17	9 A.M.		7	5.8	0

RABBIT 63; weight 2,010g.

Date	Hour	Treatment	Urine		
			Quant. cc.	Sugar	Albumin
May 17	12 M.	Piqure.			
	1.30 P.M.		20	0	0
	3		14	0	0
	4.15	Piqure.			
	7.30		14	slight	0
	9	Subcut.injection of 12cc. 80% Kahlbaum dextrose solution.	5	"	0
" 18	9.30 A.M.		10	slight	0
	2 P.M.		10	0	0
	5		6	0	0
" 19	10.30 A.M.		70	0	0

RABBIT 64; weight 2,125g.

Date	Hour	Treatment	Urine		
			Quant. cc.	Sugar	Albumin
May 17	4.15 P.M.	Piqure.			
	5.15		30	faint	Slight
	7.30		21	slight	"
	9	Subcut. injection of 13cc. 80% Kahlbaum dextrose.	5	faint	"
" 18	9.30 A.M.		2	slight	"
	2 P.M.		2 drops	faint	"

Summary for Rabbits 60, 61, 63, 64.

First, it may be noted that the glycosuria bears no relation whatever to the quantity of urine. Also, at different periods following the puncture, different quantities of dextrose were injected subcutaneously. If the puncture resulted in a diminution of the internal secretion of the pancreas, the delay was such that time was presumably allowed for this diminution to manifest itself. It is found, however, that the injected dextrose has an anti-diuretic rather than a diuretic effect, and that practically or wholly the entire dose is utilized. In the case of Rabbit 61, this dose was between 7 and 8 g. per kilo, and was injected at a time when the rabbit was excreting approximately 3 per cent dextrose in its urine. Nevertheless, we see here the same thing that is seen in every non-diabetic glycosuria; the animal even when actively engaged in excreting considerable quantities of dextrose, is still able to utilize injected dextrose. There may be a diminution of the "apparent" tolerance due to shock or some other non-specific condition, but the specific ability to utilize dextrose is unharmed. The law of summation of effects of glycosuric agencies naturally holds, *i.e.*, the dextrose injection increases the glycosuria, but the law of the paradox also holds; *i.e.*, the great bulk of the sugar is utilized, no matter how large the quantity of sugar may be. Piqûre glycosuria is what a certain school have supposed diabetes mellitus to be, viz., a pure overproduction of sugar in the liver, with no specific impairment of the power to utilize sugar. The difference from diabetes is sharp and absolute.

This difference does not mean that piqûre does not constitute a nervous shock to the pancreas. If the effect of piqûre were equivalent to removal of half or more of the pancreas, and if this effect were to be continued for several hours, it still would not be possible to demonstrate this effect in a normal animal.

Anatomical Effects.

In Dog 18 on August 14, piqûre was performed, not followed by glycosuria, though the nutritive state was excellent. Death resulted from an accident the next day, and autopsy showed the stroke to be barely below the calamus, in the closed portion of the medulla.

Dog 159, male mongrel aged 3 years, weight 9 kilos, was punctured three times on the same day, and 2 days thereafter received a subcutaneous injection of 8 g. dextrose per kilo, in order to

test whether piqûre is followed by any prolonged lowering of sugar-tolerance. Anuria and death followed; autopsy showed all three punctures perfectly placed, one behind the other just above the calamus.

Microscopic examination confirmed not only the well-known absence of changes in the liver, but also the absence of even the slightest test change in the pancreas or its islets. The adrenals of Dog 159 were not examined; those of Dog 18 showed the typical exhaustion described by Kahn and Starkenstein (without glycosuria).

DOG 54; weight 9,495g.

Date	Hour	Treatment	Urine		
			Quant. cc.	Sugar %	Albumin
May 16	2.30 P.M.	Piqure			
	4		13	Heavy	0
	5	Subcut.injection of 50cc. 80% dextrose.	4	1.82	0
	7.30		7	1.46	0
	10		5	1.95	0
" 17	9 A.M.		7	2.4	0
	5 P.M.		38	Faint	0
" 18	9 A.M.		90	0	0
	5.45 P.M.		325	0	0
" 19	9 A.M.	First Feeding	115	0	0

Summary for Dog 54.

The puncture was followed by well-marked glycosuria but not polyuria. Dextrose injected subcutaneously failed to act as a diuretic, and all or practically all was utilized. The usual secondary polyuria occurred on May 18.

The paralysis cleared up within a few days. The dog lived for months in the laboratory, was used for several experiments, and reared a litter of pups. She appeared normal in all respects except for a slight clumsiness of the hind legs which could be discovered by close observation. On October 5, pancreatic tissue weighing 11 g. was removed, leaving a remnant about each of the two ducts, each remnant estimated at 1.5 g. Though the operation was exceptionally quick and easy, the dog died the next day with asthenia and subnormal temperature, different from the appearance of simple shock or collapse, and resembling the symptoms after epinephrectomy. It is not known whether the piqûre could have contributed to this result.

DOG 58; weight 4,070g.

Date	Hour	Treatment	Urine		
			Quant. cc.	Sugar %	Albumin
June 14	2.30 P.M.	Piqure	5	slight	slight
	4 "		4	"	"
	5.15 "				
	5.45 "	50cc. 80% dextrose given by stomach tube.			
	6.30 "		3	"	faint
	8 "		2	heavy	slight
	9 "		8	5.8	"
	11 "		8	7.2	"
" 15	9.30 A.M.		45	faint	0
	1 P.M.		16	0	0
	4.30 "		10	0	0

The sugar in the above experiment was poorly absorbed. There was no attempt to vomit, but at 6:30 p.m. on June 14, the dog passed 110 cc. of liquid feces, containing 9.1 per cent dextrose. The next morning, another defecation was 120 cc., containing 2.4 per cent dextrose. Nevertheless, the absorption of most of the sugar is indicated, and the glycosuria promptly showed a great increase. There had been no polyuria, and the high percentages of glycosuria likewise produced none. The marked polyuria caused by dextrose in diabetic animals, even when they were at the point of death from weakness, was shown in Chapter VI. The contrast with piqûre is sharp.

In the earlier part of this chapter, the fact was mentioned that normal animals fail to show piqûre-glycosuria unless a certain stock of glycogen is present in the liver. Reference was also made to the findings of Thiroloix, that in animals from which all but a few milligrams of pancreas-tissue has been removed, and in which starvation has produced cessation of glycosuria, the piqûre brings about a renewal of glycosuria. It was therefore desired to learn whether my dogs with diabetes, or with diminution of pancreas-tissue almost to the point of diabetes, would behave like Thiroloix's dogs, or would follow the rule of normal animals. The following series shows that they react negatively, like normal animals.

Dog 127; male; age 1 year; weight 6860 g.

Removal of pancreatic tissue weighing 21 g. Remnant about lesser duct estimated at 0.6 g. ($\frac{1}{36}$). Diabetes gravis. Distemper. Ten days after operation, owing to sickness and refusal

of food, the weight had fallen to 4735 g., and the glycosuria, which had been 6.1 per cent on the day before, ceased. Accurate sugar-puncture caused no glycosuria. Death next day.

Dog 95; female; old; weight 6500 g.

Removal of pancreatic tissue weighing 16.1 g. Remnant about lesser duct estimated at 1.45 g. (about $\frac{1}{12}$). Polyuria and cachexia followed, without glycosuria. Twelve days after operation the weight had fallen to 5 kilos and the dog was weak. Two sugar-punctures were performed at one operation, both accurate. No glycosuria; death that evening.

Dog 87; male; age 1 year; weight 7900 g.

Removal of pancreatic tissue weighing 14 g. Remnant about main duct estimated at 2.5 g. ($\frac{1}{6}$–$\frac{1}{7}$). No diabetes. Distemper beginning a month after operation. After 3 days of sickness and fasting, sugar-puncture. Glycosuria 0.7 per cent (0.56 g.). Repeated the next day; no glycosuria. Death the day following.

Dog 71; male; adult; weight 10,500 g.

Removal of pancreatic tissue weighing 22.4 g. Remnant about main duct estimated at 9.2 g. ($\frac{1}{3}$–$\frac{1}{4}$). Distemper and refusal of food beginning 3 days after operation. More or less forcible feeding. Twelve days after operation, weight 9800 g.; 4 sugar-punctures performed in 2 operations. Death that evening. No glycosuria.

Dog 125; male; age 1 year; weight 11,300 g.

Removal of pancreatic tissue weighing 22.4 g. Remnant about main duct, perhaps also communicating with lesser duct, estimated at 2.4 g. (about $\frac{1}{10}$). Distemper; glycosuria suppressed by weakness. Twelve days after operation, weight 9600 g. Two sugar-punctures at one operation. Death next day. No glycosuria.

Dog 80; female; age 7 months; weight 4400 g.

September 1, removal of pancreatic tissue weighing 7.9 g. Two remnants left communicating with ducts; total weight estimated at 1 g. (about $\frac{1}{9}$). Diabetes levis. September 25 to October 7, starvation, followed by sugar-feeding. Dog very weak. Evidences of distemper October 13; piqûre, with accidental hemorrhage; death that evening; no glycosuria.

Summary.

All the above were partially depancreatized animals, in which piqûre was performed during distemper or some condition of malnutrition and weakness. Dog 127 was an animal with diabetes gravis; when glycosuria ceased from weakness, piqûre failed to restore it. Dog 95 developed polyuria but not glycosuria after the operation, and piqûre performed in her weakened condition caused no glycosuria. Dogs 80 and 87 were examples of diabetes levis. In none of the series was the effect of piqûre any different from what it would have been in a similarly weakened normal animal. These animals therefore behave differently from Thiroloix's dogs, which possessed only a few milligrams of pancreas-tissue.

The most important experiments of this series consisted in attempts to produce diabetes in partially depancreatized animals by means of the piqûre. The partial removal of the pancreas creates the predisposition which is suspected in most human patients. The piqûre is an irritative nervous lesion, analogous to the supposed exciting cause of traumatic diabetes.

The one notable and positive success of the series was in Dog 63. For details, reference may be made to the complete protocol in the Appendix. The animal was thin, choreic, and a trifle altered mentally in consequence of previous distemper which he passed through in this laboratory. The remnant left at the operation of June 13 was between one-fourth and one-fifth of the pancreas, *i.e.*, a size which prevents even diabetes levis. The tests performed during the starvation period of June 27 to July 5 were noted in Chapter VI (page 348). The dextrose injection of July 3 proved that the tolerance was rather low, in consequence of the combined effects of pancreas-reduction and starvation; but the test shows conclusively that the animal was not diabetic, for the injected dextrose acted as a well-marked anti-diuretic in comparison with the saline injection of June 30. This evidence was confirmed by the fact that when feeding was begun on July 5, the dog was able to eat his fill of bread-and-meat mixture without a trace of glycosuria. On this same carbohydrate-rich diet, glycosuria remained constantly absent.

On July 17, a sugar-puncture was performed, resulting in permanent paralysis of the left side and PERMANENT DIABETES GRAVIS. The urines of 3:30 and 4:15 p.m. were not tested for acetone; but it is noteworthy that the first specimen tested, at 6 p.m. (less than 4 hours after the puncture) showed a heavy acetone reaction. The typical sweet diabetic odor also appeared, and these conditions persisted throughout the animal's life, viz., diabetic odor and heavy acetone reaction, but ferric chloride test always negative. Tests for β-oxybutyric acid were never made. The sudden appearance of heavy acetonuria at the very outset, under these conditions, is a fact of possible interest for the theory of acidosis.

At first the dog was given dextrose and carbohydrate food. But on July 21 (four days after puncture), a diet of beef was begun, and it will be noted that on this diet the glycosuria ranged as high as 7 per cent. The poor appetite and other disturbances were obviously due to a return of distemper.

On July 25, starvation was begun. Glycosuria continued till the morning of July 29, though the dog was weak and emaciated. On July 29, feeding of beef brought a prompt return of glycosuria.

On August 2, a fixed routine was begun, and on August 3 a subcutaneous injection of dextrose was given. Accuracy of the test was spoiled by the extreme weakness of the animal and the vomiting of the feed and water. But though the animal was near to death, and though food and water were vomited, and though the dextrose injection was in the form of a concentrated solution, nevertheless the diuretic action of dextrose was manifest, in that the quantity of urine was almost as great as on the day preceding. The result is in striking contrast with the anti-diuretic action of dextrose in a non-diabetic animal. It leaves no doubt that the condition in this animal was true diabetes.

Death occurred the next day. A serious omission was made in the autopsy, in that the fourth ventricle was merely glanced at in order to obtain a general idea of the location of puncture. An accurate description, and sections to show the presence or absence of inflammatory change, would have been highly desirable. The pancreas remnant weighed 5.5 g., and was absolutely normal in gross appearance and consistency. As described in Chapter XXI, the microscopic changes characteristic of diabetes were present. Therefore, the condition created by an organic lesion of the nervous system here showed itself by organic changes

in the pancreas. It is conceivable that a functional change may be present in human patients without organic changes.

No other results as striking as this one have been obtained. Some of the findings however are still encouraging.

Dog 97.

Reference was made to this animal previously in this chapter.

On September 27, all but about one-eleventh of the pancreas was removed. Blocking of the duct prevented diabetes gravis, and the actual condition was merely a mild diabetes levis.

On November 6, the remnant was dissected free from everything except its vessels. The condition still remained diabetes levis. Heavy meat-feeding on November 10 and 11 (1000 g. and 1200 g. respectively) produced no glycosuria, while the subsequent carbohydrate diet resulted in considerable glycosuria (up to 3.7 per cent).

In the midst of this glycosuria, on November 14, a sugar-puncture was performed. The immediate effect (presumably upon the liver) was only a slight sugar-excretion, in the urine of November 14 and 15. But there was a later effect (presumably upon the pancreas) which was more marked, for the feeding of cooked meat, with or without raw pancreas, kept up a glycosuria which ceased only on November 20. It is noteworthy that the dog's muscular control was returning during this same period in which his carbohydrate assimilation was improving.

On November 24 another puncture was done. The immediate effect was entirely negative. But on November 27 (the usual delay when the pancreas is involved), on meat diet, a glycosuria of 1.4 per cent suddenly appeared. The next day (November 28) it was 3.6 per cent. On November 29, the urine abruptly became sugar-free, and the polyuria diminished. On November 30, a sudden change was manifest. The dog, which had been lively and only a little clumsy, was found completely paralyzed on the right side, and profusely salivated; the glycosuria simultaneously was 1.3 per cent. The occipital sinus which had been discharging cerebro-spinal fluid had become closed two or three days before. A knife now carried down into this path released a considerable quantity of clear fluid. The paralysis and weakness were such that the dog could not eat. The next day the dog was found dead, with evidences of profuse salivation during night. The post-mortem urine contained 4.2 per cent sugar.

Autopsy Record.

Thorax negative; peritoneum clean; liver large and fatty; other viscera negative. Pancreas remnant is a small mass composed of two distinct parts. One is a tiny fragment of pancreas weighing 0.2 g., in good condition and communicating with the contiguous duodenum by a small duct. The remainder of the remnant is larger and weighs 2.75 g., but this weight is practically valueless, as it represents chiefly omentum and fibrous tissue, in which are contained atrophic pancreas tissue and widely-distended ducts not communicating with bowel.

Inspection of floor of fourth ventricle shows two symmetrical punctures as perfect as could be made. Both are at the same level, a trifle above calamus scriptorius; and one is just to the right, the other just to the left of the median line. Fluid escaped in small quantity when skull was opened, and it now appears slightly turbid. The brain is crowded down so that the medulla is pressed farther than normal through the foramen magnum. The ventricles are perceptibly distended. No hemorrhage and no obvious inflammatory process in fourth ventricle.

A well-marked glycosuria began, and continued two days. On November 30 it reappeared. On this date the dog could eat nothing; yet, on starvation, the glycosuria suddenly became heavy. The autopsy the next day showed the cause of both death and glycosuria, viz., infection of the puncture wound.

Concerning this dog, the following three remarks are suggested.

First, it may be inquired how, if the pancreas remnant was "enervated" on November 6, the puncture could have any direct effect upon this remnant. A direct nervous effect is however conceivable on the following basis: (*a*) "enervation" may not have been complete; (*b*) there was still a small remnant, weighing 0.2 g., which was never "enervated" at all.

Second, it will be noted that in this dog the muscular paralysis was transient, just as the diabetes was transient. They were evidently parallel. In Dog 63, paralysis and diabetes were both permanent.

Third, the diabetes disappeared in this dog, but *when the irritative process was increased by infection*, diabetes returned. The impression is given that the irritation from the puncture alone, without infection, was not sufficiently lasting.

Dog 154.

Reference may be made to the complete protocol in the Appendix. Central and peripheral nervous lesions were combined.

In the original operation of November 24, the remnant left was between a fifth and a sixth of the pancreas. Aside from the glycosuria of December 2–5, there was no sugar-excretion, but a definite polyuria.

On December 7, nerves to the remnant were broken, without perceptible result. The remnant was not fully "enervated."

On December 15, a sugar-puncture was performed. [Autopsy later showed it well-placed.] A distinct effect was obtained, in that glycosuria continued for three days. During this time the paralysis also improved, but the glycosuria cleared up somewhat more rapidly than the paralysis.

On December 22, pancreas-tissue weighing 0.95 g. was removed. The effect was slow in coming; but after the large meal of 1500 g. meat on December 25, a slight glycosuria was found on December 26, and this proved to be permanent diabetes gravis. The result is of interest, because it will be noticed that the pancreas remnant was still unusually large; its actual weight when the dog came to autopsy (in extreme emaciation) was 4.85 g. This represents more than one-sixth of the total pancreas, in other words a fraction larger than is compatible with diabetes gravis in the absence of nervous injury. This is the only animal in which the pancreatic operation giving rise to diabetes has been *subsequent* to the piqûre; but this constitutes an interesting order of experiment, and should be given a more extended trial.

The conditions in the following dog were apparently similar, and the pancreas-remnant was smaller, yet results were negative.

Dog 148; male; age 1 year; weight 14,500 g.

November 16, removal of pancreatic tissue weighing 26.7 g. Remnant about main duct estimated at 3.3 g. (about $\frac{1}{9}$). Followed by transient diabetes gravis, polyuria, and permanent diabetes levis.

December 4, the large nerve-trunks to the remnant were broken, but it was not completely "enervated." No effect.

December 11, sugar-puncture was followed by only transitory glycosuria. The same result followed a repetition of the puncture on December 15, except that bare traces of sugar persisted in

the urine on meat diet till December 19. The dog was killed in an operation on that day, and the pancreas-remnant was found to weigh 13.3 g. This great hypertrophy may account for the failure to produce permanent diabetes gravis in this case.

DOG 28.

Female; age 2 years: weight 7,750g.

April 14, removal of pancreatic tissue weighing 20.3g. Remnant surrounding both ducts estimated at 4.5g. (1/5-1/6). No diabetes.

May 18, piqure and dextrose injection as follows.

Date	Hour	Treatment	Urine		
			Quant. cc.	Sugar	Albumin
May 18	12 M.	Piqure.			
	1.30 P.M.		50	5.2	-
	2.45 "		22	3.65	-
	3 "	Subcut. injection of 50cc. 80% dextrose.			
	4.30 "		30	10.4	-
	5.45 "		18	14.6	-
	8 "		14	10.4	-
	10 "		3	2.4	-
" 19	9 A.M.		80	4.3	-
	10.30 P.M.	100cc. 50% glucose given by stomach tube.			
	5 "		100	10.4	-
" 20	9 A.M.		70	12.	-

The above animal was not fully diabetic, as proved by the failure of dextrose to act as a diuretic. But, on the other hand, the pancreatic function appeared plainly to be breaking down, for the glycosuria increased; and especially notable is the fact that a urine-specimen of 100 cc. contained over 10 per cent dextrose, and another of 70 cc. contained 12 per cent dextrose. In normal animals, the anti-diuretic effect of dextrose is such that such large quantities of urine are practically impossible to obtain with such high percentages of sugar; and the simple nervous effect of piqûre upon the liver and kidneys seldom continues so long. Prospects seemed excellent for a permanent diabetes; but on the evening of May 19 the dog fell from a table, and the next morning was found dead from strangulation of intestine by adhesions from previous peritoneal operations.

Dog 161.

This animal was mentioned in connection with peripheral lesions. The original operation on November 29 left a duodenal

remnant and a subcutaneous graft, the latter being "enervated." Diabetes levis resulted.

On December 12, sugar-puncture was followed by only slight glycosuria, but it persisted for two days.

On December 15, a repetition of the puncture caused no glycosuria and practically no paralysis. Autopsy later showed these punctures to be well placed, close together in the floor of the ventricle, not far from the point of the calamus.

On December 21, trauma of the graft was without effect. On December 23, removal of a portion of it was followed by transient diabetes gravis.

The fact that the graft was "enervated" might possibly account for the relative failure of the punctures, because of the failure of the nervous impulse to reach this graft. The part played by the punctures in producing the transient diabetes gravis cannot be clearly estimated.

Dog 74; male; adult; weight 6670 g.

At the original operation (August 19), the remnant left was one-sixth of the pancreas. There was no diabetes, and the dog was glycosuric only on sugar-feeding.

On November 9, sugar-puncture was performed, and an accidental brain injury (not in the medulla) resulted in extensive general paralysis. Glycosuria was well-marked for two days (2.9 per cent on November 10, 1.1 per cent on November 11).

On November 14, the principal nerves to the remnant were broken, and 0.6 g. of pancreatic tissue was removed. Faint glycosuria on meat diet continued for a week. In view of the size of the pancreas-remnant, this glycosuria cannot well be accounted for except by the previous sugar-puncture.

On November 23, the piqûre was repeated, without glycosuria and with very little increase of paralysis.

On November 27, 0.35 g. more pancreas tissue was removed. Glycosuria was present the next two days. Then it ceased. The dog was found dead of low-grade peritonitis on December 3. The post-mortem urine was found to contain 0.5 per cent sugar; also the quantity of this urine (200 cc.) was unusually great for an animal's last day of life. The pancreas-remnant was found still to weigh 3.2 g., *i.e.*, more than a fifth of the original weight of the pancreas. The sugar-punctures must therefore be allowed a share in the occasional periods of glycosuria of this dog.

As noted in a previous chapter, this animal seemed to show azoturia; *i.e.*, especially on the days before and after November 20, the animal ate enormously and appeared to digest well, yet rapidly lost weight, while the urine was abundant and of high specific gravity. Circumstances did not permit nitrogen analyses to cover this point.

Dog 141; male; age 1 year; weight 10,550 g.

November 8, removal of pancreatic tissue weighing 22.9 g. Remnant about smaller duct estimated at 3.1 g. ($\frac{1}{8}$–$\frac{1}{9}$).

November 23, piqûre.

November 28, removal of 1.65 g. additional pancreatic tissue.

December 9, piqûre.

December 11, death.

No glycosuria at any time, though diet was bread. Autopsy was done hurriedly, and the question of patency of the small duct was not decided. The most probable explanation of the absence of diabetes is that the duct was accidentally obliterated at the time of operation.

Dog 145; male; age 1 year; weight 10,000 g.

November 10, removal of pancreatic tissue weighing 2.1 g. A remnant was left between the two ducts communicating with both, estimated at 3.5 g. ($\frac{1}{7}$). Transient diabetes levis.

On November 23, sugar-puncture was followed by glycosuria for two days, the amount on the second day being only a trace. But on November 28, the dog was able to take a heavy meal of bread without glycosuria.

Death occurred from operative accident on November 29. The pancreas remnant was found to weigh 7.4 g. This great hypertrophy will account for the cessation of the diabetes levis, and also for the failure of the piqûre to cause diabetes.

Dog 143; male; age 1½ years; weight 13,350 g.

November 9, removal of pancreatic tissue weighing 23.2 g. Remnant communicating with both ducts estimated at 3.7 to 4 g. (about $\frac{1}{7}$). Later operations showed that this remnant hypertrophied greatly.

November 23, a sugar-puncture was followed by no glycosuria, and the dog retained a perfect tolerance for bread. Autopsy later proved this puncture accurate.

November 29, pancreas-tissue weighing 1.8 g. was removed, followed by transient diabetes gravis on December 4–6. On December 8, another fragment weighing 1 g. was removed from the pancreas, with only a slight temporary glycosuria.

December 15, sugar-puncture (again accurate) was followed by slight glycosuria on meat diet for two days. It did not persist.

The relatively negative effects of piqûre in this animal are probably explained by the marked hypertrophy of the pancreas-remnant.

Dog 163; female; age 1 year; weight 7675 g.

December 6, removal of pancreatic tissue weighing 12.5 g. Remnant left about main duct, and another communicating with lesser duct; weight of each estimated at 2 g.; therefore total remnant = about $\frac{1}{4}$ of pancreas.

December 12, two sugar-punctures at one operation, 4 p.m. Urine record as follows:

December 12, 7 p.m., 100 cc., 3.6 per cent sugar.
December 13, 9 a.m., 30 cc., 4 per cent sugar.
December 14, 9 a.m., 60 cc., 4.1 per cent sugar.
December 15, 9 a.m., 125 cc., no sugar.

December 16, death from another puncture with too large an instrument. It was hoped by increasing the extent of brain-injury to produce a greater or more lasting effect. Aside from the fatal result in this animal, this attempt in other dogs has given no better results than the ordinary puncture. At autopsy in this animal, the smaller pancreas-remnant weighed 3 g., the larger 7.6 g. This great hypertrophy is sufficient to explain the failure of piqûre to produce diabetes.

Dog 164; female; age 5 years; weight 9750 g.

December 6, removal of pancreatic tissue weighing 16.3 g. Remnant about main duct estimated at 4 g. (about $\frac{1}{5}$). No diabetes.

December 19, piqûre, later shown by autopsy to be in closed portion of medulla, in median line, barely below calamus. Glycosuria continued till December 23, the highest percentage being 1.2 per cent. The dog would not eat, but was fed forcibly a little meat each day. December 24, urine became sugar-free. December 25, dog found dead. Pancreas-remnant weighed 5.3 g.

This is one of the series in which an unduly broad instrument was used; the weakness and early death outweigh the advantage.

Remarks.

Omitting Dog 63, the series still indicates rather plainly the tendency of the piqûre to give rise to glycosuria persisting for several days on meat diet in partially depancreatized animals. The relation of the condition to nervous injuries in predisposed human patients is evident. In all these cases, failure to obtain a truly permanent diabetes may be accounted for by the following three facts.

1. The damage or irritation resulting from the piqûre is not sufficiently lasting. The muscular paralysis clears up rapidly, and the glycosuria clears up in a somewhat parallel manner.

2. In some cases great hypertrophy of the pancreas-remnant occurs, and the predisposition is then no longer sufficient for success in this sort of experiments.

3. In many of the animals used, there had also been one or more operations to test the effects of local nerve-injury, in which all or most of the nerves to the pancreas-remnant had been destroyed. This combination is of interest, and the negative results speak somewhat for the irritative as opposed to the paralytic explanation of the effects of piqûre; for if the effect were paralytic, then the combination of central and peripheral lesions should increase the paralysis. Also, if the influence upon the pancreas were humoral, *e.g.*, from the adrenals, the destruction of pancreatic nerves should be without effect. But the discharge which exhausts the adrenals is prompt, like the effect upon the liver, and recovery follows soon; whereas the true diabetes due to pancreatic disturbance is often delayed for several days. In Dog 63, the most successful example, the adrenals were found thoroughly normal at autopsy; the only changes were in the pancreas. There is accordingly no evidence for a humoral mechanism in this condition, and the main process seems to be a direct nervous action upon the pancreas. It is therefore highly desirable to use dogs in which the nerves to the pancreas-remnant are intact. Dog 63 was such a dog, and I regret that circumstances prevented extending the series.

Irrespective of any results or considerations, however promising, in other animals, the case of Dog 63 stands as a perfect example and a demonstration in itself. It matters not whether

the animal was peculiarly predisposed by distemper (chorea, mental changes), or whether some special irritation or even infection at the site of puncture led to the result, or whether such a result can be reproduced in other animals; the fact remains that the strictest requirements laid down by Kausch for human cases were here experimentally fulfilled. The animal was not diabetic before the puncture, and it was diabetic after the puncture. Therefore even if an exception, it corresponds strictly to the exceptional human patient who develops traumatic diabetes.

But as a matter of fact, this case need not stand as an exception. The rest of the series speaks too plainly on this point. I am confident that by making use of suitable methods in suitably predisposed animals, permanent diabetes can be produced in a considerable proportion of cases. The following two methods are to be especially recommended.

1. Piqûre may be performed simultaneously with the partial removal of the pancreas. There seems to be some evidence that the pancreas at this time is in a specially labile condition. It will thus perhaps be found that diabetes can be produced with larger pancreatic remnants than otherwise. At least, cases that would have been transient diabetes gravis should be thus convertible into the permanent form, and diabetes gravis may even be obtained in cases that might otherwise have been only diabetes levis.

2. More important should be the experiments with lesions involving greater irritation than the piqûre. Kahler's silver-nitrate method should here be serviceable. It should be feasible to expose the desired region and inject silver nitrate under guidance of the eye into the medullary "sugar-centre," into Eckhard's "lobus hydruricus et diabeticus," and other desired locations. Other irritants may also prove serviceable; for example, lycopodium powder or croton oil, used by Arthaud and Butte (1). Perhaps none is to be more highly recommended than (living or dead) tubercle bacilli or some similar infectious agent. A certain clinical condition, viz., tubercle of certain nerve-areas in connection with diabetes, is thus imitated.

Such experiments have a theoretical interest with respect to the nature of diabetes. If an irritative condition of the sympathetic system is back of diabetes in some cases, the possibility is opened up that a similar condition is behind the general mass of cases, *i.e.*, that diabetes is ordinarily an irritative condition of the sympathetic. It may then prove to be to some extent a

matter of accident whether this irritative condition manifests itself chiefly by an effect upon the pancreas as diabetes, or chiefly by an effect upon the kidney as nephritis, or chiefly by an effect upon some other organ as gout or hepatic cirrhosis or some other disease. Returning from this speculation, we come to the practical lesson that if diabetes is an irritative condition of the abdominal sympathetic, therapeutic methods may then come into use, which have as their purpose the doing away with those nervous elements which are keeping up the pernicious irritation. This conception of sympathetic irritation has been suggested by various evidence noticed from time to time in this chapter. It is an idea that already exists in the literature; it agrees well with the long-recognized benefits of opium [see Naunyn, p. 435, also Gigon's paper], it agrees with Loewi's discovery of adrenalin-mydriasis, and explains satisfactorily the production of clinical and experimental diabetes by nervous injuries.

C. Emotional.

My experiments concerning possible emotional influences in the production of experimental diabetes have turned out uniformly negative. For the sake of brevity, the results in cats may be summarized as follows.

In a long series of animals, the fact has been confirmed that simple tying on a comfortable holder may cause glycosuria, which in general varies with the degree of excitement, and may be absent altogether when the cats are too quiet. As is well known, polyuria may accompany the glycosuria. My cats as a rule were gentle, therefore the glycosuria was always below 2 per cent, and polyuria was never marked, generally absent.

In one animal, the urine obtained by emptying the bladder at the end of tying was sugar-free, but that secreted after returning to its accustomed cage showed a decided reaction.

Removal of one adrenal has no effect upon emotional glycosuria. When the second (left) adrenal is removed by a quick easy operation, the animal no longer shows emotional glycosuria, — a fact already published from Cannon's laboratory. In one cat, piqûre was performed after removal of the second adrenal; the puncture was accurate, but not only glycosuria but also polyuria and salivation were absent. The absence of glycosuria agrees with some of the negative results in Wertheimer and Battez's

series. The greater difficulty of producing glycosuria in all these cases is well explained by the findings of Gautrelet and Thomas as a simple alteration of the nervous condition. The absence of polyuria and salivation, unless accidental, indicates that the effect is in no way specific for the sugar economy, but probably extends equally to the entire sympathetic domain.

Emotional glycosuria is increased by subcutaneous injection of dextrose. Also, the apparent tolerance is greatly lowered. By repeated experiments with suitable gentle cats, it is demonstrable that glycosuria may remain absent every time a given animal is tied, and be present every time the tying is accompanied by a small dextrose injection. The dose required to produce glycosuria under these conditions may be as low as 1 g. per kilo or less.

Dextrose still acts as an anti-diuretic, and the paradoxical law holds as usual; *i.e.*, the real tolerance is infinite; the vastly greater portion of every dose is utilized, irrespective how large the dose. Therefore the condition is not diabetes. Nevertheless, it is not justifiable to interpret the condition as an effect upon any one or two organs. There is presumably a general excitement of the sympathetic system. The pancreas may well be included in the effect. But a disturbance of this degree, acting upon the pancreas for only a few hours, could not possibly produce any result demonstrable by any test of the internal function in a normal animal.

The only hope of positive results must lie in using animals predisposed to diabetes. But as noted in Chapter X, a series of cats in which I removed most of the pancreas died; and even when pancreatectomy is nearly complete, cachexia is more prominent than glycosuria. My attempts to make use of predisposed cats therefore failed.

Dogs.

Authors have described emotional glycosuria in a few dogs with this idiosyncrasy, and presumably hyperglycemia results in all dogs; but emotional glycosuria does not occur in normal dogs. The following records are typical of a series of negative experiments. The most nervous animals possible were chosen for all the experiments.

Dog 21 (see protocol).

On March 16, this nervous dog was subjected to the combined effects of bondage, anæsthesia, etc., and intravenous injec-

tion of dextrose. An effect upon the tolerance or diuresis was especially looked for. Neither of these was appreciably altered. A slight glycosuria persisted longer than in a normal animal, but the anæsthetic alone would account for this. There is no change indicating a diabetic tendency, and no effect of emotion is perceptible at all.

Tests of the tolerance by means of the subcutaneous method were not made in dogs. More or less lowering of the apparent tolerance by emotional disturbance is to be expected.

Dog 34; female; age 2 years; weight 6390 g; full-fed, fat and normal.

February 17, the dog was tied for 3 hours, from 2 to 5 p.m., and worried. The dog was of very nervous disposition, and showed fright and distress. The urine during the entire 3 hours was only 12 cc., sugar-free; that the next morning was 110 cc., also sugar-free.

March 15, a similar procedure was adopted, but the dog remained tied for 6 hours, from 11 a.m. to 5 p.m. In addition, an intravenous injection of 4 g. dextrose per kilo was given at 11:15 a.m. Urine record:

Hour	Quantity cc.	Sugar, per cent	Hour	Quantity cc.	Sugar, per cent
12 M.	252	3.2	2 P.M.	3	0.45
12:30 P.M.	16	7.3	5 P.M.	10	Slight
1 P.M.	2	0.3	8:15 P.M.	40	Neg.

The excretion was therefore practically the same as under normal conditions, except that a trace of glycosuria perhaps persisted a trifle longer than usual. The principal feature watched for was the secondary oliguria. This was found to occur, during persistence of the glycosuria, just as is normal; this is in contrast to what is found in diabetes.

Dog 32; female; age 2 years; weight 6425 g.

Removal of pancreatic tissue weighing 12.4 g. Remnant with intact vascular supply left about lesser duct, estimated to weigh 1.8 g. ($\frac{1}{7}$–$\frac{1}{8}$). Duct accidentally obliterated, with consequent atrophy, as shown by autopsy. No diabetes; fair sugar-tolerance.

Two weeks after operation, the dog was tied for three hours, and in other ways a maximum of excitement maintained during the whole time. The dog at the close appeared exhausted. Urine for entire period 25 cc., sp. gr. 1050, sugar-free. Repeated catheterizations showed that the urine diminished instead of increasing during the experiment.

Dog 114; female; age 1½ years; weight 9600 g.

Removal of pancreatic tissue weighing 17.2 g. Remnant about lesser duct estimated at 2.4 g. (about ⅛). Transient diabetes levis. Six days after operation, the glycosuria on bread diet had fallen to 0.8 per cent and was evidently on the point of disappearing. On that day the dog was whipped for biting. On the next day, the urine was found sugar-free nevertheless.

In a few other bad-tempered animals on the verge of diabetes, the effect of whipping has been observed, and there has never been glycosuria.

Dogs 80 and 86 were partially depancreatized animals previously described in this chapter. The effect of prolonged tying was tested in them under various diets and conditions, and no glycosuric effect was ever found.

Dog 74 was also previously mentioned. On September 22, during a period of slight glycosuria on bread-and-meat diet, the dog was tied for 3 hours, and the same was repeated the next day. Though agitation was notable, there was no increase of glycosuria, and on September 24, just after the last bondage, the urine became sugar-free.

The salivation which generally follows piqûre is well known. It seems not to have been observed that when a dog has apparently recovered entirely, a return of salivation can be produced in some cases by subjecting the animal to excitement. This susceptibility may persist at least for several weeks. This fact gave the hint that perhaps excitement might also result in special manifestations of pancreatic disturbance. Lepine [(1), p. 495] notes that saliva is increased in certain human cases of "cerebral" diabetes. Tests were therefore made in three of the animals previously described in connection with central and peripheral lesions. The results were negative, as follows.

Dog 143, after having previously undergone partial pancreatectomy and piqûre, on December 19 was tied for 3½ hours. The

dog was much worried and profusely salivated, but there was no glycosuria.

Dog 154 (see protocol), after previous partial pancreatectomy and piqûre, on December 19 was tied on back for $3\frac{1}{2}$ hours. Dog was of quiet disposition; there was no worrying and no salivation, also no glycosuria.

Dog 161, after previous partial pancreatectomy and piqûre, on December 19 was tied for $3\frac{1}{2}$ hours. There was intense salivation but no glycosuria. Also on December 29–30, the dog spent an entire 24 hours worrying over a change of cage, but an existing glycosuria was actually diminished, because eating was less.

Remarks.

Emotion seems to be without influence upon the glycosuria of partially depancreatized dogs, with or without central or peripheral lesions of the nervous system. We may perhaps reason that though these animals have suffered various organic injuries, the fundamental constitution of their nervous system is still sound. The human patient who becomes diabetic in consequence of psychic stress has presumably a nervous system which is fundamentally unsound and liable to functional troubles which we do not understand.

Prospects of success from such experiments appear absent in dogs. If cats could be made available, or if some species could be found which combines the emotional peculiarities of the cat with the pancreatic peculiarities of the dog, the chances might perhaps be better.

Conclusion.

I believe there is evidence to justify the hypothesis that human diabetes is in most cases a functional disease of the nervous system, manifesting itself especially by its effect upon the pancreas. A classification of diabetes on the basis of severity has been already presented. Another classification on the basis of etiology is now suggested, as follows:

Diabetes ..... { Organic.
Nervous..... { Peripheral.
Central.

The term organic here refers solely to the pancreas; if the origin of the disease is nervous, it is perhaps immaterial to the

pancreas whether the exciting cause is a functional or organic change in the nervous system. Organic diabetes would therefore include only a small minority of cases, namely, those in which the diabetes results from infection through the ducts, or from some equally positive destructive process.

Nervous diabetes would include the great majority of cases of the disease. In a few instances the nervous disturbance seems to be of peripheral origin, but in the great majority it is probably central. In a later chapter will be taken up the subject of islet changes. It seems established that in numerous cases of diabetes, such changes cannot be demonstrated; and in most other cases I am disposed to refer the islet changes to the underlying nervous cause; otherwise why are the islets diseased? Distinctions cannot be absolutely sharp till our knowledge is further increased; for example, shall the cases due to arteriosclerotic changes in the pancreas be classified as organic, or shall we refer the arteriosclerosis back to a nervous cause, perhaps including arteriosclerosis among the diseases of the sympathetic system? Such finer distinctions and speculations may be left to the future. For present practical purposes, it seems desirable to direct attention to two conceptions. One is not new; it is that diabetes is a functional disease of the nervous system, probably of the sympathetic system. The other is new; it is that the average diabetic patient perhaps has almost as good a pancreas as anybody's, and that his pancreas may do its normal work if relieved of abnormal influences which interfere with it. That the disturbance of the pancreas is — at least at the outset — functional in nature, and that the pancreas itself is — largely or entirely — organically sound, is a conception which not only agrees better than any other with certain known facts concerning the disease, but also introduces the hope of therapeutic mastery over it.

CHAPTER XVIII.

MISCELLANEOUS ATTEMPTS AT DIABETIC THERAPY.

THE general trend of the ensuing chapters will be toward procedures which stand in some possible relation with diabetic therapy. It therefore becomes pertinent to inquire whether there is any evidence to show that diabetes may be curable, and to examine into various proposals concerning the treatment of the disease.

1. Curability of Diabetes.

The opinions of authorities on the subject are reviewed by Leo (2). From Seegen he quotes the following: "I never saw a diabetic who could indulge in carbohydrate like a well person without the appearance of sugar in the urine, and in whom an improvement of this sort continued for any long time." Likewise v. Mering is quoted; "I have never been able to determine that a diabetic could permanently assimilate carbohydrate in equal manner with a normal person; *i.e.*, in other words, I have never seen a genuinely cured diabetic." Most of the others quoted by Leo either deny the curability of diabetes, or express a belief in rare cures on evidence that is open to question.

Lepine [(1), p. 621] enumerates Seegen, v. Mering, Rumpf, and Leo as the ones who contest the curability of diabetes, and Külz, Senator, Frerichs, and Ebstein as holding other views. Lepine ranges himself "without hesitation" among the latter group. Recovery is uncommon, but it may occur.

Von Noorden takes a conservative attitude, but reports cases of cured diabetes in his own experience.

The text which gives fullest consideration to the cure of diabetes is that of Naunyn. He believes unqualifiedly in the occasional complete disappearance of the disease. He says on page 384: "Diabetes mellitus may recover, but this happens very seldom, and I know of no case in which the cure of the disease has occurred after any long duration; only among cases of traumatic diabetes are found a few which recovered after more than

three months." Náunyn looks upon the replacement of diabetes by some other disease as totally different from true recovery.

In judging the question, account must be taken of differences and peculiarities in the course of the disease. Some confusion has arisen because of the extreme mildness of some cases of diabetes, and because of the intermittent course in other cases. The characteristics to be expected of the disease under various conditions are instructively tabulated by von Noorden [(1), pp. 248–49] from the standpoint of prognosis. In general, the following are *favorable prognostic indications:*

1. Advanced age at beginning of the disease.
2. Long standing of the disease without serious emaciation or complications.
3. Traumatic cause of the diabetes (somatic or psychic trauma).
4. Syphilitic origin of the diabetes.
5. Occurrence of exclusively mild forms of diabetes in the patient's family.
6. Preceding and accompanying obesity.
7. Accompanying uric acid diathesis and gout.
8. Slight intensity of the glycosuria; tolerance for certain moderate quantities of carbohydrate.
9. Wide variations and gradual increase of the tolerance for carbohydrate.
10. Low values of acetone bodies and ammonia in the urine.
11. Favorable environment, which permits following dietetic and hygienic requirements.
12. A fasting respiratory quotient above 0.73. This indicates a stock of glycogen, which in severe cases is exhausted. Also increase of the quotient by carbohydrate ingestion is favorable (Benedict and Joslin).

The following are *unfavorable prognostic indications:*

1. Youth of the patient; especially childhood.
2. Great loss of strength in spite of brief duration of the disease.
3. Occurrence of severe forms of diabetes in the family.
4. Early appearance of serious intercurrent and complicating conditions, especially pulmonary tuberculosis, acute infectious diseases, and pregnancy.

5. High intensity of the glycosuria; low tolerance for carbohydrate; low respiratory quotient (below 0.73 fasting). Stubborn resistance of the glycosuria to dietetic treatment.

6. Unfavorable environment (necessity of hard labor; difficulty in following diet).

7. Heavy excretion of acetone and ammonia.

8. Excretion of oxybutyric acid. Coma.

One source of disagreement regarding the curability of diabetes has consisted in the understanding of what constitutes a cure. Some authors have been willing to speak of a cure when a patient was able to return to ordinary mixed diet. Cantani (ref. by Leo) even specified "moderate quantities" of carbohydrate. Leo insists on the test that the *largest quantities* of *starch* shall cause no glycosuria. Lepine [(1), p. 621] opposes such a test; he considers it on a par with calling every person a dyspeptic who has any inconvenience from the largest quantity of any food. Again, there is a question of duration. If a diabetic becomes sugar-free on mixed diet, but after months or years shows the typical disease again, is it a recrudescence of the same diabetes, or was the patient temporarily cured while merely the diabetic diathesis or tendency persisted? The safest judgment of these questions is the strictest. A diabetic who can assimilate a considerable quantity of carbohydrate is greatly improved, but he is not cured so long as tests can reveal signs of the disease, and is certainly not cured if starch diet produces glycosuria. Also, the only real cure is a permanent cure; after five or ten years one can begin to judge. Otherwise, where shall the line be drawn? A mild diabetic may assimilate a mixed diet for a few days, a few weeks, a few months, sometimes a few years. But if the diabetes returns, where is the fundamental distinction between days and years, and who shall decide the precise number of days of sugar-freedom which shall constitute this sort of "cure"? A cured diabetic, then, is one who can go and live like other people on the ordinary quantities of starch and sugar, and remain permanently free from his former disease. A diabetic "cured" on any other basis may at any moment relapse into severe diabetes, which may sometimes end in coma within a few days after its onset.

By such a test, numerous alleged cures are ruled out. The supposed transitions between diabetes mellitus and insipidus, as described by Teschemacher (1) and other authors, are probably

explainable as a mild pancreatic involvement which manifests itself partly by polyuria, or as very mild and intermittent diabetes mellitus complicated by diabetes insipidus. One of the most striking of intermittent cases is that reported by Leo (2). Diabetes with 2½ per cent glycosuria was diagnosed in a patient in 1901. It disappeared after a period of treatment, and the patient was sugar-free on mixed diet till 1903. He then felt a renewal of thirst and weakness, lost 16 pounds weight, and was found to be excreting 6 per cent dextrose, or 225 g. per day. He was again placed on restricted diet, and in May and July of 1904 was able to live on mixed diet without glycosuria; in particular, there was no sugar-excretion from a combination of 400 g. bread, 500 g. potatoes and 100 g. sugar, and various test-meals eaten in the presence of the physician were equally well assimilated. But in October the diabetic symptoms returned, with glycosuria of 5.2 per cent. On restricted diet the patient again improved, and was able to assimilate 300 g. bread daily. This was the condition at the time of reporting the case. This patient therefore presents no cure of diabetes; he merely exemplifies No. 9 of the "favorable prognostic indications" of von Noorden's list (above), viz., wide variations of carbohydrate tolerance, and increase of the same. The variations and the increase of the tolerance are merely somewhat greater than ordinary.

Teschemacher (2) describes a somewhat similar case in a woman, who became diabetic after a pregnancy, recovered on treatment and remained sugar-free on mixed diet for 6 years, then after another pregnancy developed a more severe diabetes and died two years thereafter in coma. Another woman (elderly) with a glycosuria of 6 per cent recovered sufficiently that she could assimilate a liberal ration of carbohydrate. She lived thus for a number of years, till her death from other causes. During this period she was constantly sugar-free, except during slight febrile attacks due to bronchial or intestinal catarrh. The moderate glycosuria induced by the fever ceased promptly with the end of the fever each time. In other words, the patient was constantly diabetic, but the disease was extraordinarily mild.

Cases of genuinely cured diabetes are however occasionally reported and demonstrated by incontestable evidence. On the basis of such testimony, it may be said that recovery is possible in three sorts of cases:

A. Acute diabetes arising from a curable cause.

B. Rare cases in children.

C. Diabetes in association with certain other morbid conditions.

A. Acute Diabetes Arising from a Curable Cause.

Naunyn (p. 384) states that a better chance of cure than in other forms of diabetes may be hoped for in those cases which spring from a curable organic disease. Again (p. 93) he properly rejects the attempts of some authors to mark off "transient nervous glycosuria" as distinct from diabetes, on the sole ground that they recover. Transient nervous glycosuria undoubtedly exists. But many of the transitory cases reported bear the earmarks not of simple glycosuria but of diabetes. As noted in the previous chapter, nervous glycosuria as represented by the piqûre may produce both glycosuria and polyuria, but it alone does not lower the carbohydrate tolerance very greatly, nor does it cause dextrose to become a diuretic. The application of these tests to such cases of acute transient diabetes may be expected to establish their diabetic genuineness and thus the genuineness of the cure. The cases of acute diabetes with recovery may be divided into (I) traumatic and (II) infectious.

(I) Traumatic. In this category is properly included the diabetes following apoplexy, for the cerebral hemorrhage is from the present standpoint essentially a trauma. The following may be mentioned as representative cases of this group.

Naunyn (p. 80) quotes the following from Kämnitz. A girl of 17 years, with severe contusion of the head; thirst, polyuria, but glycosuria only after 8 days (1 per cent). In the course of several weeks the glycosuria increased to 2.3 per cent, then gradually diminished and by the end of three months had disappeared. Thirst and polyuria of 4–6 litres persisted. Naunyn also quotes from Plagges the following. An injury of the head in a 16-year-old boy. Heavy glycosuria, which ceased after 2 or 3 weeks. Polyuria outlasted the glycosuria by two months. From Scheuplein, Naunyn quotes the following. A fall from a height, with luxation of a thoracic vertebra. On the fifteenth day thereafter appeared diabetes; later marked increase of urine and sugar. As result of dietetic régime, no sugar after 43rd day. Transition into diabetes insipidus. Two years after the accident, no symptom of diabetes.

The above cases were hardly observed long enough to conform to the requirements for demonstration of a cure. But a question need not be raised on this point, for it is agreed by authors that a number of cases of traumatic diabetes do recover completely

and permanently. On this basis the traumatic is the most hopeful form of diabetes. It must also be remembered however that the greater number do not recover, but go on to death, according to Weiland, within three months to five years; that also, according to Naunyn, recovery is very rare after the disease has lasted for 3 months. Apparently when diabetes persists for a certain length of time, a "diabetic habit" is formed, which persists even though the original cause may disappear.

Pflüger [(1), p. 399] quotes the following case from Frerichs. A man aged 58, after a severe eye-operation, developed trigeminal neuralgia and general cutaneous hyperæsthesia. Soon afterward, there was tachycardia, thirst, and glycosuria of 5 per cent, with polyuria of 8–10 litres daily. The condition improved on a Carlsbad treatment, and sugar disappeared. Frerichs saw the man 8 years later, and tested the urine repeatedly without finding a trace of sugar. Cutaneous hyperæsthesia still persisted, but the diabetes was permanently cured.

Pflüger also takes from Frerichs the following case. A man aged 54 suffered a sudden apoplectic attack, with disturbance of articulation, right facial paresis and great thirst. The urine was 5–6 litres, containing 3 per cent sugar. On anti-diabetic diet and other routine, the paralysis gradually cleared up, and in 3 months after the attack the glycosuria disappeared. Three years later the patient was still well. Then another apoplexy caused death.

(II) Infections. Among the favorable prognostic indications listed by von Noorden, No. 3 consists in a syphilitic origin of the disease. Diabetes of such origin is frequently improved by anti-syphilitic treatment. In a minority of cases a permanent cure may be obtained; presumably here the syphilis is cured before too great damage is done to the nervous system, and before a premanent functional or organic change of the pancreas has been produced. Cures of this sort are described by Naunyn (p. 145) as follows.

From Lemonnier: A man aged 49, diabetic for 5 months; glycosuria 7 per cent; no improvement on diet. Syphilitic ulcer in the throat. Disappearance of both syphilitic and diabetic symptoms after four weeks of anti-syphilitic treatment without restriction of diet. Absence of glycosuria was demonstrated by frequent tests during the following 11 months.

From Manchot: A man aged 38, without hereditary taint; in 1897 an indurated sore on the lower lip, healed by inunction. Later in 1897, syphilis of skin and mucous membranes; an abortion of his wife. No thirst or other symptoms noticed. In June, 1898, gummatous ulcers of tonsils; gumma of soft palate, later perforating; urine 2700 cc., sugar 2.5 per cent, no albumin. Anti-syphilitic treatment cleared up the diabetes, so that the patient could take mixed diet, drink beer, and assimilate 100 g. dextrose.

Other cases are described more briefly by Naunyn in this same place.

The rare cases of cured diabetes in connection with gall-stones may here be mentioned.

Naunyn (p. 63) describes a patient aged 59, with symptoms of cholelithiasis for several years. In 1894, after some weeks of pain in the region of the liver, there was glycosuria of 0.7–1 per cent, with daily urine of 2 litres. On moderately restricted diet the sugar disappeared, but returned in traces if the bread ration surpassed 150 g. Since that time the patient has lived on mixed diet, and up to 1904, quantitatively determinable sugar has not appeared in the urine. Naunyn remarks that the evidence of cure is not absolute in this case.

A genuine cure of the above sort is however not improbable. Naunyn classifies these and other cases as diabetes due to liver disease. In one sense doubtless the liver disease is the cause of the diabetes. But since the liver itself has nothing to do with diabetes one way or the other, the only way in which it can ever be the cause of diabetes is through its proximity to the pancreas. It is probable that a gall-stone attack may set up an organic disturbance in the pancreas, especially through the agency of infected bile. If the cholelithiasis improves, it is possible that the pancreas may recover a sufficient degree of function to prevent diabetes. Such a patient may be like a dog from which three-fourths or four-fifths of the pancreas has been removed; there may be a permanent lowering of sugar-tolerance, but yet no tendency to diabetes.

Garrod (2) reports the following case.

A man aged 58 presented general symptoms of chronic cholelithiasis, without colic. The urine contained bile, no albumin, but 2.8 per cent dextrose. Later tests showed glycosuria as high as 4.9 per cent. Anti-diabetic diet reduced the glycosuria as low as 0.48 per cent, but did not abolish it. The jaundice and other symptoms gradually cleared up, and the patient was allowed small quantities of bread. Glycosuria disappeared within a few weeks, and the patient lived sugar-free for two years on mixed diet, and 100 g. dextrose taken fasting was perfectly assimilated. Later, however, traces of sugar reappeared in certain specimens of urine, so that the diabetes cannot be considered permanently cured.

It would appear as though operative interference in a case of this sort might have yielded favorable results. Such operative success in connection with other cases is referred to by Garrod [(2), p. 561].

The part played by local pancreatic infection is clearly indicated in other cases described by Garrod, in connection with mumps. He quotes from Harris an instance in which diabetes in a man was discovered within a month following mumps. From

Finizio is quoted a report of acute pancreatitis with steatorrhea following mumps, and from Barbieri the following case.

A boy aged 6 contracted mumps during an epidemic. Six days after the onset he complained of umbilical pain and tenderness, and had vomiting and diarrhea. There was slight fever, and the stools were pale and fatty. The daily urine was 2400 cc., free from albumin, containing sugar which was not quantitatively estimated. Within two weeks the glycosuria and all other symptoms had disappeared and the urine had diminished to 600 cc.

A condition of this sort is just what should be expected if mumps ever does in the "abdominal salivary gland" what it does in the parotid. A prompt recovery from the diabetes is also not surprising.

Funck [(1) and especially (2)] has described the almost miraculous clearing up of diabetes under treatment directed to the intestine. It is claimed that the cure of chronic colitis and enteritis has resulted in disappearance of diabetic symptoms and restoration of full carbohydrate tolerance. Such cases must necessarily be few, and the permanency of the cures also needs to be assured. But the possibility must be acknowledged that infection of the bowel might extend up the pancreatic ducts and give rise to diabetes, which might disappear if the infective process were checked before too late. Tests of pancreatic digestion do not necessarily rule out a pancreatic infection.

The case reported by Richartz, of attacks of diarrhea in association with glycosuria as high as 1.4 per cent, also suggests the possibility of pancreatic infection. Treatment of the intestinal condition removed not only it but also the glycosuria. The patient could then assimilate bread in any quantity desired, but as little as 30 g. dextrose produced glycosuria. It is of interest that this patient came of diabetic family. Three possibilities are suggested: (*a*) the case was a mild transient diabetes resulting from pancreas-infection; (*b*) the patient had an inherited weakness of carbohydrate assimilation, and a non-specific illness resulted in glycosuria; (*c*) the patient had a latent diabetes throughout, and it was temporarily aggravated by the illness. Cure is not certain.

Hürter reported the following case.

A girl aged 10 years, of healthy parentage but with some diabetic relatives. She and two others of her family suffered at the same time from an attack of diarrhea with urticaria. The child had several such attacks, also one with vomiting; and immediately after the latter, hunger, thirst and polyuria became prominent. She

lost weight, and sugar was found in the urine in the third week. Physical examination was negative. The glycosuria was as high as 9 per cent, and a slight ferric chloride test was present. On dietetic treatment the sugar-excretion diminished from 210 g. to 10 g. in 24 hours, and soon after disappeared. The child gained weight, and after 7 months was able to take 420 g. bread or 50 g. dextrose without glycosuria. Sugar-freedom has continued on mixed diet.

The possibility of a pancreatic infection is here suggested, and cannot be ruled out by digestion tests.

In previous chapters has been mentioned the easy glycosuria e saccharo and occasional glycosuria ex amylo in febrile patients, *e.g.*, in pneumonia. Von Noorden [(1), p. 33] considers that such cases represent a temporary true diabetes, due to a transient disturbance of the pancreatic function by intoxication or infection. More accurate tests will doubtless show that for the average cases of this sort, this view is untenable. An involvement of the pancreas is indeed conceivable in any acute infectious disease. Such an example seems to be the case of scarlatina described by Zinn [ref. by Naunyn, p. 141]. The glycosuria here was found after recovery from scarlatina; two weeks thereafter it was 1 per cent on meat diet, four weeks thereafter 0.25 per cent, and after another four weeks it was absent even on mixed diet. The permanency of the cure was assured by observations covering several months. The responsibility of the scarlatina for the diabetes is probable, and the cure is fairly certain. Holsti [ref. by Naunyn, p. 367] reported a somewhat similar case after influenza. It is another example of cured diabetes. The average case of febrile glycosuria is fundamentally different from this. It is ordinarily a simple toxic glycosuria. The patient's "apparent" tolerance is reduced, but he is not in the slightest degree diabetic because there is no specific involvement of the pancreas. Tests of all these ordinary cases may be expected to show that dextrose is not a diuretic, and that the *true* tolerance of the patient is as high as anybody's.

The same may be said concerning most alcoholics. As shown in Chapter XIV, animals may have their dextrose tolerance reduced somewhat by simultaneous toxic doses of alcohol, but the resulting glycosuria bears no relation to diabetes. Likewise the simple glycosuria of delirium tremens and most alcoholic conditions is of merely toxic character. But as alcohol in some human patients leads to hepatic disease, so also in a smaller number it may apparently lead to pancreatic disease. A certain

degree of acute pancreatic disturbance may sometimes be present in acute alcoholism, and a chronic disturbance also appears sometimes possible. Presumably predisposition is important. The condition may sometimes be curable, as in the following case described by Naunyn (p. 77).

A physician aged 51 years, alcoholic, without hereditary taint. Consulted Naunyn in 1896 for alcoholic neuritis; urine sugar-free. In 1897 the leg-pains returned, along with cyanosis, dyspnea, pleuritic exudate, slight œdema of legs, and other signs of cardiac weakness. Various changes in reflexes and reactions. The urine contained a trifle of albumin and 5 per cent sugar; on a glass of beer and very little bread daily it was still 1 per cent. On routine treatment the sugar disappeared within a few days, and recovery was complete. With abstinence from alcohol, the patient attended to a large practice, ate starch and sugar at will, and was sugar-free under these conditions in 1904.

It may be admitted that such a case probably contained an element of diabetes, and that cure was probably complete.

B. Rare Cases in Children.

Diabetes in childhood is recognized as an especially malign condition. Youthfulness of the patient is placed first among the unfavorable prognostic indications in von Noorden's list. Nevertheless, there are on record a few instances of complete and permanent cure of diabetes in children.

Von Noorden [(1), p. 244] reports the following example from his own experience.

He treated a 7-year-old boy who on strict diet constantly excreted 20–30 g. sugar and considerable quantities of acetone bodies. He became sugar-free only by intercalation of oat- and vegetable-days. He remained on restricted diet for some years. Von Noorden saw him again at the age of 12, when he was in perfect health, eating the ordinary diet of the household without a trace of glycosuria.

Richard Schmitz [ref. by Naunyn (p. 385) also by Garrod (2) and by Leo (2)] reported three cases of cured diabetes in children. One of them was the following.

A girl of four years, whose mother and sister were diabetic, suffered an attack of acute "gastric fever." The child's urine had been repeatedly found free from sugar, and a test four days before this attack was negative. In consequence of the attack, a glycosuria of 5.8 per cent developed. On anti-diabetic diet the sugar disappeared in 17 days, and the child was soon able to take mixed diet. Thereafter, starches and sweets were eaten *ad libitum* without glycosuria. The girl married at 18 years, bore children, and never showed a sign of diabetes during the 20 years Schmitz had her under observation.

Schmitz' case may have originated in an acute pancreas-infection. Both of these are remarkable, Schmitz' because of the familial diabetes, and von Noorden's because of the severity of the disease. It is possible that certain recuperative or regenerative powers are greater in children than in adults, and thus a cure may be rendered more perfect when it does come. But it seems also possible that the pancreas of children is more vulnerable than that of adults, and that acute infections from the intestine or blood more easily give rise to transitory diabetes.

Teschemacher (2) has reported several cases of apparently cured diabetes. The most remarkable feature is the simultaneous occurrence of diabetes in all four members of a family, father, mother and two young children. It is doubtless a coincidence rather than an evidence of infectiousness of diabetes. The father slowly became worse; the mother and both children apparently recovered completely; they at any rate remained sugar-free on mixed diet for two years.

C. Diabetes in Association with Certain Other Morbid Conditions.

The associated disorders which sometimes alter the course of diabetes are especially (I) nervous diseases, (II) cancer involving the pancreas, (III) cirrhosis of the liver, (IV) nephritis. Gout and arteriosclerosis have some claims to a place in this list.

(I) Diabetes may occur in the course of progressive nervous disease, probably in consequence of the nervous changes, and may disappear completely with the further progress of the disease. Naunyn (p. 74) describes such occurrences in tabes. Patients who at first require several days of strict diet in order to become sugar-free, later are able to live on carbohydrate-rich diet without glycosuria.

(II) Cancer and similar disorders of the pancreas must be considered in Chapter XXII. It has long been a source of surprise and of some misconceptions, that glycosuria or diabetes is so rare in connection with cancer or atrophy of the pancreas. Practically the entire organ can be destroyed, without the production of diabetes. Reference will also be made later to the reports of authors, especially Teleky (1), of cases of diabetes which have ceased with the development of cancer. Patients who formerly were not sugar-free on strict diet, later become able

to subsist principally upon carbohydrate without a trace of glycosuria.

(III) Cirrhosis of the liver may modify or supplant diabetes. Naunyn (p. 59) reports liver troubles as relatively frequent in connection with diabetes in private practice, and in only one case (bronzed diabetes) was the diabetes severe. In hospital practice the combination is rarer, because the patients there encountered are generally in later stages, when the diabetes is already suppressed. Claude Bernard [(3), p. 355] described the case of a diabetic who later developed cirrhosis of the liver, with complete disappearance of the diabetes. Lepine [(1), pp. 427 and 621] recognizes such cases, and also accepts cachexia as the explanation. He mentions also two cases of simple cachexia, without cirrhosis, in which obese diabetics lost their fat and their diabetes, and lived for years in an emaciated condition. [Like dogs after certain pancreas operations.]

(IV) Nephritis is probably the most commonly reported condition which brings an end to diabetes. Naunyn (pp. 182–83) describes such cases, and here, and also on page 132 and elsewhere, attributes the change to cachexia. Von Noorden [(1), p. 109] refers to reports of Frerichs, Stocvis and Fürbringer in this connection, and describes a case of his own, as follows.

> Man aged 53, with a brother dead of diabetic gangrene, and a nephew suffering from a light form of the disease. Glycosuria was discovered in 1895; with moderate limitation of carbohydrate it was 1–1.5 per cent, and must have existed for some time, for diabetic cataract and neuro-retinitis were already present. Frequent examinations showed absence of albuminuria. Albumin was first discovered in traces in the summer of 1897. After a Carlsbad cure in 1898 the sugar disappeared and the albumin increased. Thereafter the patient ate daily large quantities of carbohydrate, including sugar, and even in tests with ingestion of specially large amounts, glycosuria remained absent. The typical symptoms of granular kidney developed, and death resulted in 1902, without recurrence of glycosuria.

Like most authors, von Noorden does not view the transformation into nephritis as a favorable change. The nephritis which develops (to be distinguished carefully from the harmless diabetic albuminuria) is generally of severe type; the diabetes might be palliated by treatment, but the nephritis cannot be. Vas considers nephritis a harmful complication of diabetes, and calls attention to the fact that in some cases nephritis comes on and the diabetes persists nevertheless. Naunyn (p. 211) has observed not infrequently an *alternation* of glycosuria and albuminuria,

in some cases the albuminuria coming to predominate so that the glycosuria permanently disappears. Gout and arteriosclerosis are supposed to injure nutrition and conduce to albuminuria, thus diminishing glycosuria. Lepine [(1), p. 551] describes this same alternation of glycosuria and albuminuria.

Teschemacher (2) has reported one of the most interesting cases of transition.

The proprietor of a foundry, aged 57, consulted him in 1899 for diabetes. Some years previously he had been struck in the testis by the heavy iron head of a hammer. Symptoms of diabetes were not noticed till several years after the accident, so there is no proof that the case was traumatic diabetes. After 75 g. bread the 24-hour urine was 2300 cc., containing 2.7 per cent sugar, no acetone and no albumin. After five weeks of treatment the patient was sugar-free on a regime including 150 g. bread with potatoes and vegetables in addition. The patient returned home, and had his urine examined at first every 6 weeks, later every 3 months; on full general diet it was constantly sugar-free. In 1906 the analyses showed traces of albumin. Teschemacher saw the patient again in 1909, this time with the signs of advanced nephritis. A meal containing much sugar led to no glycosuria, but the albuminuria was 0.2 per cent, with granular casts.

Three explanations for these remarkable inter-relations of morbid conditions may be considered.

First, glycosuria may cease because of impaired excretory power. It is a fact that in nephritis the kidney may become less permeable to sugar, and thus marked hyperglycemia be present without glycosuria. It is also a fact that extreme weakness in diabetic patients or dogs may interfere with elimination of sugar. But impaired excretory power is not the correct explanation in the cases we are considering. When the diabetic cannot excrete sugar properly, it accumulates in his tissues and fluids. Such a possibility is excluded in these patients, sometimes by blood-analyses, sometimes by the fact that large quantities of carbohydrate are consumed every day for long periods of time.

Second, there is the possibility that these patients merely chanced to recover a certain degree of tolerance, as other patients sometimes do, and that the association of this increase of tolerance with the onset of some intercurrent disease, such as nephritis, is purely fortuitous. Against this view, it can only be urged that the associations in question are sufficiently frequent and striking that they have impressed all authorities as representing some genuine connection; also that the improvement of the diabetes occurs apparently under conditions specially unfavorable, viz., when the patient is weakened by a new disease; and that the

cases of alternation of glycosuria and albuminuria in the same patient are difficult to explain as mere accident.

Third, there is the cachectic explanation. The intercurrent disease is supposed to produce a state of weakness, with impairment of all bodily powers, and also loss of appetite with diminished food-intake. It is seen that all the varied conditions above described have this element of cachexia in common, and cachexia, irrespective of its cause, is supposed to stop the glycosuria. It is a fact that tolerance generally increases when the food is cut down, and the cutting down of protein in some cases enables the patient to assimilate a considerably increased quantity of carbohydrate. But it is equally true that this proposed explanation violates known facts in connection with these conditions. In the first place, cachexia does *not* increase the sugar-tolerance. Cachexia invariably and necessarily lowers the tolerance, just as it lowers other bodily powers. In the second place, advanced weakness and even complications have no constant influence upon the glycosuria in diabetes. Dogs with diabetes gravis may be emaciated to skeletons and too weak to stand on their feet, but they excrete sugar nevertheless. The same may occur in human diabetics; sometimes the extreme weakness preceding death may stop the glycosuria, but everybody knows how weak and cachectic the ordinary diabetic may become, while still excreting large quantities of sugar. Furthermore, it is known that infectious diseases, and diabetic gangrene, and other complications which exhaust the patient far more than incipient nephritis, may exist with heavy glycosuria and certainly with no benefit to the sugar-tolerance. In the third place, it is not a fact that cachexia accounts for the increase of tolerance in the patients we are considering. Teleky expressly excludes it in his report concerning cancer, and the nephritic cases clearly exclude it. When sugar and albumin alternate in the same patient's urine, nobody has ever claimed any remarkable cachexia during the albumin periods. In von Noorden's nephritic patient, described above, the diabetes was discovered in 1895; the first traces of albumin appeared in 1897; glycosuria disappeared in 1898; thereafter the patient could assimilate perfectly as much starch or sugar as he chose to eat; and he did not die till 1902. Numerous such cases are reported. Sometimes the patients were glycosuric on strictest diet; after the complication set in, they were able to take carbohydrate in abundance without showing a trace of sugar; and they lived for

weeks, months, even years in this condition. To explain such relations on the basis of mere cachexia is obviously impossible.

A fresh explanation in agreement with the facts therefore seems desirable. If we accept diabetes as a (probably functional) disease of the nervous system, it is not surprising that progressive nervous disease should, at some stage, give rise to diabetes; nor that with advance of the disease the nervous conditions should change (irritative perhaps becoming paralytic), so that the diabetes comes to an end. Changes of this character are in fact the rule in progressive nervous diseases. In a similar manner, some alteration in the splanchnic nervous regulation results in morbid conditions in other organs, *e.g.*, liver or kidneys, and the alteration may be such that the disturbance in the pancreas persists (*i.e.*, diabetes coexists with nephritis or cirrhosis), or the seat of disturbance may be shifted from the pancreas to one of these other organs, so that the diabetes disappears. This evidence points toward a functional rather than an organic nervous disturbance, because of the ease with which it can shift. An occasional shift of this sort in the same patient need not be surprising, when it is considered that diabetes, nephritis and related conditions frequently occur in the same families, apparently as different manifestations of the same diathesis. The relation of cancer to these transformations may appear most doubtful, but will be studied in detail in later chapters.

When diabetes is supplanted by some other morbid manifestation, the two generally blend at first, so that the patient during a certain period exhibits, for example, diabetes plus nephritis. The case of Teschemacher is interesting in that the changes are separate; the patient is first diabetic; his diabetes disappears (probably slowly, though the finer changes cannot be followed); he is free from obvious disease for several years; then comes the slow onset of nephritis. Some underlying nervous disturbance here apparently manifested itself in two different forms, and the transition from one to the other was very slow, with a symptom-free period between. The step beyond this is when for some reason the nervous disturbance clears up entirely; the diabetes vanishes, and no other disease takes its place. The traumatic and apoplectic cases point to a nervous cause and a nervous cure. If we could imitate the process, diabetes would be a curable disease.

The general lesson which we learn therefore is, first, that dia-

betes is sometimes cured by nature; second, that when nature performs the cure, the method is to make the patient's own pancreas resume its function. This agrees with the idea expressed in the preceding chapter, that the average diabetic may have a pancreas which is practically as good as anybody's. It is able to recover its lost functions if the conditions are made favorable. These favorable conditions are occasionally afforded by some spontaneous process, which may be associated with unfavorable changes in other organs, or may be independent of such changes. It is as usual our wisest plan to seek to imitate the method whereby nature achieves the desired results. As regards the cure of diabetes, this method will be to induce the patient's own pancreas to resume the function of internal secretion, which it is presumably able to perform.

Such a method will be suggested by experiments in later chapters. It is desired in this chapter to discuss certain therapeutic attempts, old and new, for the sake of the light which they throw upon the general question.

2. Levulose.

The literature concerning levulose, and experiments with normal animals, were presented in former chapters. According to a view once published by von Noorden [(3), p. 546], levulose which is converted into glycogen in the diabetic liver is useless, because it is returned to the blood as dextrose and the latter excreted. Only the levulose which passes through the liver and reaches the other tissues as such is utilized in diabetes. In Chapter II, on the contrary, it was noted that the liver is the principal organ of levulose metabolism. But, if this early idea of von Noorden were correct, the best way to give levulose to the diabetic would be subcutaneously (or intravenously), for by this means the smallest proportion of levulose goes to the liver and the largest proportion to the other organs. The only levulose injection in my series of diabetic animals was mentioned in Chapter VI, in connection with diuresis. This was in Dog 64, on July 27. From a therapeutic standpoint the result was not favorable. There was not the great and immediate diuresis and increase of nitrogen excretion which follows a similar injection of dextrose; on the contrary there was considerable retention. But there was increased sugar excretion and especially on the morning of July 29, the secondary

diuresis brought with it a considerable excess of nitrogen. Furthermore the dog's behavior was carefully noted, and it was evident that the effect of the levulose injection was bad, not good. As previously mentioned, parenteral sugar injections do not diminish acidosis even in non-diabetic subjects. Levulose injections have been proved in clinical practice to be unavailing as a treatment for coma. There are therefore no therapeutic prospects in this direction. Experimentally, there are some points of decided interest; for it may perhaps be found that dogs of the type which I have described differ from totally depancreatized dogs and more closely resemble human patients in their behavior toward levulose.

3. Glycogen.

The literature concerning glycogen, and experiments with normal animals, were considered in Chapter II. It was found (Rolly, Pflüger) that glycogen is somehow so important to the animal that when fasting it will even use up protein for the building of glycogen. Glycogen injected parenterally in normal animals is partly or wholly broken down; part of it is excreted as sugar and dextrin. It may be somewhat toxic when injected in large quantities, but the toxicity is not great.

The diabetic is known to be as a rule poorly supplied with glycogen. So-called theories of diabetes have been based on the assumption that there is either a lack of the normal power to form or to fix glycogen, or an excessive destruction of glycogen. Some slight attempts at a glycogen therapy of diabetes have been made. Laumonier claimed that small glycogen injections diminish the glycosuria and improve the general condition of diabetic patients. Cohen refers to "Dr. Pettit of Paris" as having reported excellent results from the administration of 1 *or* 2 *grains* 3 or 4 times a day.

It seemed desirable to test the effects of glycogen injections in diabetic animals. From the therapeutic standpoint, one might reason, "The animal lacks glycogen; therefore give it glycogen." The only way of giving glycogen as such is by parenteral injection, since glycogen given by mouth reaches the tissues as sugar. There is a question whether the cells can absorb and utilize glycogen as such from the blood; there are also the indications that glycogen is broken down rather than utilized as such after injection in normal animals. Moscati's claim that starch is picked up,

stored and metabolized as such by the cells, would bespeak a similar possibility for glycogen; but as previously noted, Moscati's findings have been seriously questioned. Grube proved dextrin to be a direct glycogen-former; curiously, it seems never to have been determined whether glycogen forms glycogen. Aside from the therapeutic is a certain degree of theoretical interest. Some writers in the past have supposed that the diastatic power of diabetics is diminished; they have tried to increase it by injections of diastase. Others on the contrary have imagined that some substance is circulating which breaks down the glycogen with excessive rapidity. The finding of dextrin and maltose in diabetic urine might be interpreted either way. In the injection of glycogen or dextrin, we have a test for these notions, which is probably better than the customary tests of the diastatic power of fluids and extracts postmortem. As the utilization of injected sugars was compared, it is now of interest to compare the utilization of higher carbohydrates in diabetic and non-diabetic animals. If the power to form glycogen is lacking, there is the possibility that injected glycogen may supply a specific need. If on the other hand some circulating substance is breaking down the body-glycogen, it may be that this substance will spend its force upon the injected glycogen or dextrin, thus sparing the body-glycogen.

Dog 19 (normal weight 8–9 kilos), an animal with diabetes gravis, received subcutaneous glycogen injections as follows: on March 9, 2 g.; on March 10, 5 g.; on April 6, 25 g.; also on April 1, 25 g. dextrin. The small glycogen injections of March 9 and 10 produced no distinct effect one way or the other. Following the larger injections of dextrin on April 1 and of glycogen on April 6, there was an apparent gain of weight, but it was due to retention of water. There was no specific difference in the effects of dextrin and of glycogen. Nitrogen was not spared, and glycosuria was not diminished. Dextrin appeared in the urine as it does in normal animals; the qualitative tests were similar, and quantitative comparisons were deemed unprofitable. There seems to be no difference in the diastatic power of the diabetic and normal animal as judged by parenteral injection, just as there is no difference in the diastatic action of their tissues and fluids postmortem. Observation of the animal showed that the small injections were without benefit and the large ones were distinctly harmful.

4. Diastase, Yeast, and other Substances.

In Chapter II, reference was made to the researches [cf. Ehrmann and Wohlgemuth, who review the literature] proving that the diastase-content of the blood of the pancreatico-duodenal vein is not higher than that of other vessels. No justification for a ferment-therapy has been found, yet the attempts with it have been so numerous that nothing like a full review of the literature will be undertaken here.

Wynhausen (1), also Leschke (1), refer to Kussmaul, who in 1874 thought he observed benefit from intravenous injections of diastase in diabetic patients. Lepine [ref. by Naunyn, p. 440] recommended a "glycolytic ferment" prepared from malt-diastase. But Lepine[(1), p. 365] reports negative results from the intravenous injection of yeast extract (Buchner method) in depancreatized dogs, and also (p. 683) finds no benefit from yeast-extract or invertin. Leschke (1) has destructively criticized all such attempts. Hildebrand proved that injection of diastase lowers the dextrose-tolerance [naturally, because of toxicity]. Von Noorden [(1), p. 263] mentions Leo's recommendation of the pressure-extract of yeast, also the use of zymase tablets (Fermocyl). Recently Seemann has claimed a little benefit from the giving of Fermocyl tablets, but as the reviewer (Dtsch. med. Wchnschr.) justly says, the same sort of results have been claimed for every anti-diabetic remedy. Naunyn and von Noorden (l.c.) both admit the possibility that the yeast might act by fermenting carbohydrate food in the intestine; supposedly the fermentation products might be assimilated with nutritive benefit. But practical results have not been attained.

Of other substances, it might perhaps be easier to enumerate those that have not been tried than those that have been tried in diabetic therapy. Von Noorden (p. 262) refers to the former use of thyroid tablets, iodothyrin, etc. The baseless idea that the adrenals are concerned in diabetes has given rise to attempted therapeutic use of adrenal extract, and to the suggestion of the use of the serum or milk of epinephrectomized animals. Von Noorden also refers to the rectal injections of aqueous extracts of calf-liver by Carnot and Gilbert, and Brunton's experiments with muscle-extract; Charrier used intestinal juice in vain; Lorand recommended Rodagen; Menyhért devised keratin-coated pills of proteolytic ferment, lipolytic ferment and alkali.

Lepine [(1), p. 364] tried intravenous injections of peptones in depancreatized dogs.

In the interpretation of results, mistakes have arisen from over-hopefulness on the part of the experimenter, accidental variations in the glycosuria or other symptoms, and the toxic effects of some of the substances used, which diminished glycosuria by diminishing either the appetite, the sugar-production, or the permeability of the kidney. The laws governing these changes are not fully understood. Toxicity of the substance or prostration of the patient are not the sole factors. Compare for example the varying effects of fever, toxins and infectious diseases [Nebelthau. Von Noorden (1), p. 106 ff]. Experimentation with every conceivable therapeutic agent in such a hopeless disease has been commendable. But the failure of all agents of the above classes may now be recorded as complete, and further attempts with such substances, at least in human patients, are unjustifiable.

Mention of the numerous drugs used at different times for diabetes will be omitted. Probably no other among them has ever yielded results equal to those of opium. Opium does not cure diabetes, but its beneficial effects in suitable cases may be reasonably explained on the assumption that it temporarily diminishes the irritability of the abdominal sympathetic.

5. Lecithin.

In a subject where such free rein has been given to the imagination, it is rather surprising that greater attention has not been given to lecithin. A lecithin-therapy is more strongly suggested than many things that have been tried. We might justify such an attempt on the following grounds.

(A) Lecithin is a constituent of every living cell. Its precise status and function are unknown, but the fact that it contains nitrogen, phosphorus and fat should confirm its importance. Koch has written a paper on the significance of lecithin for the cell. Buchmann gives the literature up to 1904. Landberg has covered the subject exhaustively from the theoretical and therapeutic standpoint, and gives 203 references to the literature. Danilewsky found both lecithin and cholesterin to be powerful heart-stimulants. The most recent review of the subject is by Peritz, who advocates lecithin therapy for various disorders.

(B) Lecithin forms some sort of compound, complex, or intimate mixture with dextrose. Jecorin, discovered by Drechsel,

has given rise to discussion which is not yet ended. Bing was unable to find lecithin-increase when the sugar of the blood was increased, but his method was intravenous injection, which was unsuitable. For details of the subject, reference may be made to the work of P. Mayer (2 and 3), also that of A. Mayer and Terroine, and of Siegfried and Mark. By mixing lecithin and dextrose under suitable conditions *in vitro*, a product can be obtained which is more or less closely identical with the natural jecorin; for distinction it is commonly referred to as sugar-lecithin. Porges and Neubauer consider these substances to be mere mixtures. Baskoff (1 and 2) looks upon them as true but somewhat indefinite compounds. Other opinions are similarly at variance.

(C) If any known substance represents to our minds what a side-chain or amboceptor should be, lecithin is such a substance. Chemically and physically its possibilities seem almost unlimited. It partakes of the nature of a fat, it enters into compounds or complexes with sugar and protein, it must have some part in the phosphorus and nitrogen metabolism, it combines to form various salts, and its physical possibilities as respects solution and precipitation are emphasized by Koch. Bang (1*A*) and Lapidus attribute to lecithin important influence on the action of diastase, but Starkenstein (1 and 2) and Minami have disputed this opinion. Kyes made the discovery that lecithin activates venom. Much study has been devoted to the subject; references may be found in the more recent publications of Meyerstein, and of McFarland and Weston. Küttner found that the action of both pancreatic and gastric juice is sometimes hastened, sometimes delayed by lecithin, under unknown conditions. Usuki found the digestion of fat to be hastened by lecithin. Kalaboukoff and Terroine came to negative results throughout; they found no accelerating effect of lecithin upon any of the ferments for any classes of foods, and rejected the view that the lecithin of the bile, for example, is of any importance in this connection. Michaelis and Rona (1) investigated the solubilities of albumoses and ferments as influenced by lecithin, and refer to the finding of Overton, that the salts of certain dye-stuffs are not soluble in chloroform or toluol, but become so on addition of lecithin; also to that of Kyes, that venom can be brought into solution in chloroform by means of lecithin. By such alterations of solubility, of surface-tension, etc., it is conceivable that lecithin plays an important

part in the metabolism of cells, and, incidentally, in their carbohydrate metabolism.

(D) There is room here for another "antagonism." Biedl [(3), p. 265] refers to investigations demonstrating the notably high cholesterin content of the adrenals. It is known that cholesterin in some respects stands in opposition to lecithin; for example, it may inhibit the action of lecithin upon ferments or venom, and Minz has found that it withdraws the toxolecithid from solution. Also, one of the important decomposition-products of lecithin is cholin. Considerable study has been devoted of late to the function of cholin in the body [see Pal (2), and Gautrelet (44)]; and in particular it has been set in opposition to adrenalin. For example, Frank and Isaac (2) assert that adrenalin stimulates the sympathetic and cholin the autonomic nervous system.

(E) The economy of lecithin, also of cholesterin, is actually disturbed in diabetes. In Chapter VII, diabetic lipemia was described, and was found to be essentially a lipoidemia; and the abnormal quantity of lecithin and cholesterin circulating in the blood is somehow derived from the body-cells. Erben (1 and 2) reported a diminished content of lecithin and cholesterin in the red corpuscles of diabetic blood, but his finding has not been confirmed. Peritz, however, has found a deficiency of lecithin in the tissues in diabetes and certain other diseases.

(F) Danilewski (ref. by Hatai) found that frog-eggs placed in water containing $\frac{1}{1500}$ by weight of lecithin, gained in 54 days 300 per cent more weight than those in ordinary water. Hatai experimented with young white rats, receiving lecithin by mouth or subcutaneously [or decomposition products subcutaneously? for it is stated that the injected emulsion was sterilized by *boiling*.] The gain in weight in the test rats was 60 per cent greater than in the controls, with a correspondingly greater weight of the nervous system. The diseases in which Peritz reports deficiency of lecithin are diabetes, syphilis, and nervous diseases. Through lecithin therefore we have a possible link between diabetes and two diseases known to be frequently associated with it.

(G) Berkeley in 1908 claimed benefit from the administration of lecithin in exophthalmic goitre, also in nervous patients; it is said to bring quietness, comfort, gain in weight and amelioration of symptoms. Some of the authors previously mentioned likewise considered it valuable; for example, Peritz recommends lecithin injections as a prophylactic against tabes and paralysis.

Lancereaux and Paulesco claimed benefit from lecithin feeding in diabetes. The feeding method is rational, since it has been proved that lecithin may be absorbed as such and may enrich the nitrogen and phosphorus stores of the body. Slowtzoff first discovered that though lecithin can be saponified by the steapsin of the pancreatic juice, yet part of it is absorbed as such and can be demonstrated in the lymph. Franchini found that lecithin feeding of rabbits increases the lecithin content of the liver and muscles, but not of the brain. The increased lecithin content of the liver persists for as long as 15 days after cessation of the feeding. Glycerophosphoric acid is increased in the liver and muscles. There is increase of lecithin in the feces. In the urine is a small amount of glycerophosphoric acid; no cholin, but formic acid derived from cholin.

Experiments.

The substance used was a commercial preparation of "purest lecithin." Although "lecithin" is a generic term, including various phosphatids, and different ones predominate in different organs and different animal species, the above preparation is of the sort ordinarily used in therapeutic attempts, and seemed as suitable as anything for the present purpose.

It seems never to have been determined whether lecithin is able at all to spare protein nitrogen. In Chapter IV, experiments with rats showed that subcutaneous injections of lecithin, with or without dextrose, do not prolong life in starvation. In the case of several normal dogs, especially during fasting, I have given intravenous injections of 1 or 2 g. lecithin, alone, or mixed with dextrose or saccharose. If a lecithin injection is given rapidly, a dog acts as if in pain, whining and showing general disturbance; but with slow injection there are no symptoms. The above doses of lecithin have had no perceptible effect upon the nitrogen excretion. The time-limits of saccharose excretion seem to be not materially altered. The doses of dextrose used with the lecithin have been generally 4 g., *i.e.*, somewhat above the limit of intravenous tolerance for the size of dogs used. The urine and the amount of dextrose excreted have been slightly less with lecithin than without; but the differences are fractional and lie within the limits of accidental variation.

The only lecithin injection in a diabetic animal was in Dog 49, which on June 1 received 3 g. lecithin in 30 cc. distilled water,

intravenously in thirty minutes time. There were no nitrogen analyses, but the injection had not the slightest beneficial effect upon the glycosuria or the general condition. It is improbable that diabetes consists in a lack of lecithin, or that the internal secretion of the pancreas can be either replaced or stimulated by lecithin. The experiments offer no hope for a lecithin therapy of diabetes.

6. Pancreas Preparations.

All authorities are agreed upon the failure of pancreatic opotherapy in diabetes. The attempts are continued because of the strong theoretical inducements.

A. Pancreas Feeding.

Sandmeyer (2) made the surprising discovery that feeding of fresh pancreas actually tends to glycosuria. Partially depancreatized dogs, in which atrophy of the pancreatic remnant had not proceeded quite to the point of diabetes, developed well-marked glycosuria when pancreas was added to their diet. In dogs already glycosuric, the sugar-excretion was increased 3 to 14 fold by pancreas feeding, and ketonuria was augmented. Pflüger (13) confirmed these results. In Chapter IX, the literature of this subject was reviewed, especially the nteresting work of Reach, which has shown that any meat, if *raw*, has much the same action as raw pancreas.

The attempts to treat human diabetes by pancreas feeding have been numerous and varied. Wood reported subjective improvement but increase of the sugar-excretion by 7–10 per cent. Mackenzie gave half an ounce of pancreas three times a day with negative results. Hale White fed pancreas with no benefit and with an increase of glycosuria resulting. Wills and likewise Sibley found the usual subjective mprovement [probably due to suggestion], with no change in sugar-excretion. Marshall with use of pancreatin observed a decided increase of sugar-excretion.

Rennie in 1903 reported concerning the existence of isolated pancreatic islet-tissue in teleosteal fishes, separate from the acinar tissue. Rennie and Fraser took advantage of this peculiarity to feed patients with this pure islet-tissue, without admixture of other portions of the gland. The substance was too toxic for injection purposes. The results were negative.

Moore, Edie and Abram advocated the use of secretin for diabetes, and Crofton claimed improvement in a patient on pancreatic extract with secretin. The further reports of Dakin and Ransom, Bainbridge and Beddard, and of Foster, show that the treatment is ineffective. While well conceived from one standpoint, the error lies in directing attention to the external secretion of the pancreas. If there is any relation between the internal and external secretions, it is one of opposition.

The only positive results on record from pancreas feeding in dogs are those of Pratt and Spooner. They concern especially one animal [their dog No. 5] in which the pancreas was entirely separated from the duodenum. Observations are reported extending over a year and a half. In consequence of pancreatic atrophy, the dextrose tolerance by mouth fell as low as 1.2 g. per kilo; it varied somewhat, but the upper limit was only about 6 g. per kilo, as compared with an average of 11.5 g. per kilo in these authors' normal animals. As a result of six weeks of daily feeding with fresh pancreas, the tolerance steadily rose till it stood above normal. The elevation of tolerance persisted after the stopping of pancreas feeding; the highest limit, 16.9 g. per kilo, is in fact recorded a month after the end of the feeding. The record closes about six weeks after the end of feeding, with the animal in excellent condition and the tolerance standing above 15.3 g. per kilo. The authors have later continued such experiments, and have obtained confirmatory results. The record of the dog's weight shows that improved nutrition is not the explanation. Accidental spontaneous variations in the tolerance of dogs in this condition undoubtedly exist, and need to be ruled out by a considerable number of experiments before general conclusions can be founded. The experiments are necessarily long and tedious, and much time is required for the completion of a sufficient series. Our knowledge on this subject is still so imperfect that no results backed by definite figures can be called impossible. It may be that under certain conditions pancreas feeding may produce positive effects which are impossible under other conditions. The stage at which feeding is begun, and the condition of the gland, atrophic or otherwise, may perhaps be found determining factors [Chapter XXII].

In the therapy of clinical diabetes, pancreas feeding has proved of benefit only in the organic form of the disease. Here the patient suffers from lack of the external as well as the internal

secretion of the pancreas; he loses much of the ingested food through the fatty diarrheal stools, and probably also is further injured through poisoning from intestinal decomposition. Any given influence is apt to injure a diabetic more than a normal individual, and the injury is likely to affect him in his weak point, viz., his diabetes. Probably the benefits resulting from pancreas feeding are largely thus explained. For example, E. Meyer (2) has reported decided benefit from the use of pankreon in a case of this character; the absorption of food and consequently the nutrition were improved, while the glycosuria was diminished. A more specific explanation is not entirely excluded. Wegele reported one case in which glycosuria entirely disappeared on pancreas feeding; this again was a case of pancreatic atrophy.

Apparently no one has ever tried the interesting possibility of feeding the glands of new-born or fœtal animals, in which the islets have a relatively high development and little external secretion is present.

B. Pancreas Injections.

Though pancreas feeding may have at least a digestive value in some cases of diabetes, injections of pancreatic preparations have proved both useless and harmful. The failure began with Minkowski, and has continued to the present without an exception.

A few more or less favorable claims have indeed been published. Leschke (1) reviews the erroneous reports of Capparelli concerning alleged benefit from intraperitoneal injection of fresh pancreas emulsion in depancreatized dogs, of Battistini concerning improvement in human diabetes from injections of glycerin extract of pancreas, and of Vanni concerning diminution of glycosuria in depancreatized dogs from injections of pancreas extract. Also Vahlen (1 and 2) claimed to have prepared from the pancreas a substance without glycolytic power in itself, but able to accelerate alcoholic fermentation; it diminished phloridzin or adrenalin glycosuria, and was not tried in diabetes. E. L. Scott has reported conservatively concerning a slight diminution of glycosuria in depancreatized dogs from intravenous injection of an aqueous extract of the pancreas; but his findings are doubtless explained by renal or other non-specific changes. In the papers of Zuelzer (5) and of Zuelzer, Dohrn and Marxer, it was alleged that if the

pancreas at the height of digestion is subjected to stasis for 1–1½ hours, then removed and its extract freed from albumin, the resulting product contains a "hormone" which neutralizes the glycosuric action of adrenalin and diminishes the glycosuria in depancreatized dogs and diabetic human patients. The injections were given intravenously. Forschbach (2) found a temporary diminution of the sugar excretion in diabetic dogs and patients, but no genuine benefit. The drop in sugar is evidently due to systemic and renal injury, and the treatment had to be abandoned because of toxic effects. Improved sugar-utilization, as observed by Knowlton and Starling in perfusion experiments, has not been obtainable from pancreatic extracts in living diabetic animals or persons.

The negative reports have been numerous and trustworthy. Minkowski observed no benefit from pancreatic therapy. Hedon [Travaux de physiologie, Paris, 1898] injected sterilized pancreatic extract subcutaneously and intravenously, and when this failed, he tried glycerin extracts and other preparations, all without avail; the dogs were harmed and not benefited. The findings of Gley [ref. by Biedl (3)] were also negative. In diabetic human patients, Williamson found no benefit from pancreatic preparations injected intravenously or intraperitoneally, and Hale White's results from subcutaneous injection were similarly negative. Tiberti and Franchetti (1 and 2) followed a commendable experimental method, in that they used incompletely depancreatized dogs; the milder type of diabetes in such animals perhaps allows a more accurate observation of possible slight effects, such as might be lost amid the rush of symptoms following total pancreatectomy. They obtained entirely negative results from subcutaneous injections of aqueous extracts or nucleoproteid preparations of the pancreas. Pariset (1 and 2) observed glycosuria from injection of pancreatic juice either into the portal or into the systemic veins of normal animals.

This last point has been taken up by Leschke (1). He has reviewed much of the literature concerning pancreatic opotherapy, and has pointed out that as a rule the sugar excretion of diabetics has been actually increased thereby, whether the pancreas preparations were fed or injected parenterally. Leschke therefore followed up the question experimentally. His first series consisted of depancreatized frogs. On the chance that other investigators, working with dogs or human patients, had not used suffi-

ciently large quantities of pancreas, Leschke injected his frogs (intraperitoneally, sometimes subcutaneously) with fresh aqueous extract representing one entire pancreas for each hour. Under these massive doses, the test frogs showed heavier glycosuria than the controls, and died in 1 to 3 days, while the controls died in 4 to 7 days. Pancreas extract inactivated by heating to 70–80 degrees to destroy the ferments was without such effects. In normal frogs and normal guinea-pigs, injections of fresh pancreas-extract produced glycosuria, at least to the extent of a Worm-Müller "green reaction." Repetitions of the injection led to death within a few days. Pancreas extract heated to 70 degrees was found to have slight or doubtful effect upon normal animals, and that heated to 100 degrees was entirely inert. Leschke undertakes to use his findings as an argument against the theory of pancreatic internal secretion. His more moderate conclusions are, however, fully justified; viz., that the internal secretion of the pancreas cannot be demonstrated by injections of the extract; and that treatment of diabetes by means of the ordinary extracts is not feasible, because even if an antidiabetic substance is present, the benefit from it is overbalanced by the ill effects of other substances present. In Leschke's opinion the glycosuric and toxic action of pancreas extract is due to the contained ferments.

It is a matter of some importance to decide whether the production of glycosuria is a property specific to the pancreas. If specific, the action is of decided theoretical importance; if non-specific, it has no such importance. The natural assumption is that it is non-specific and without theoretical significance. For not only did Pariset find glycosuria from injections of pancreatic juice, but other authors, for example Lepine and Boulud (3), obtained glycosuria from injections of extracts of various organs.

To test the question, I undertook subcutaneous injections of a number of organ extracts. No standarization was attempted. The method of preparation was as follows. A normal cat was etherized, then bled to death from the carotid. The liver, two kidneys, spleen, pancreas, heart, lungs and a quantity of skeletal muscle were removed and ground up separately with saline solution containing $7\frac{1}{2}$ per cent glycerin. To the liver was added 400 cc. of the solution, and to each of the other organs a quantity which on a rough guess seemed proportional to its substance. After standing on ice for 24 hours for more thorough extraction, each extract was filtered through cloth and thereafter preserved

on ice. The entire process from beginning to end was carried out with the fullest asepsis possible. No sterilization was therefore needed, and abscesses from the injections were no more frequent than ordinarily found after injections of sterile blood and other albuminous substances.

In a second series, the extracts were prepared without strict asepsis and without glycerin, and were drawn first through paper and then through a Berkefeld filter. In a third series, the extracts were prepared from the organs of a cat, which were removed from the body immediately after death from epinephrectomy. In Chapter III it was shown that subcutaneous injections of glycerin do not cause glycosuria in cats; and in the present experiments, the second series mentioned serves to exclude it as a possible contributing cause.

Eight normal cats received the injections, and each was treated with at least two different extracts, in order to rule out individual peculiarities. Judging by the behavior of the animals, the pancreas extract was most painful, presumably because of the external secretion. Repeated doses were given, slowly increasing up to 15 cc., with negative results. Then injections of 50 cc. were given, and approximately equal glycosuria was obtained from liver, pancreas, spleen, lungs and muscle. The differences were fractional and obviously accidental. Thus, spleen happened to give the minimum value (0.48 per cent) and also the maximum value (1.6 per cent) of the series. Injections of pancreas similarly in different animals gave results of 1 per cent and 1.4 per cent. Polyuria was absent, albuminuria absent or slight. The two notable exceptions to the rule were kidney and heart. These were negative for glycosuria, though each of them was tested in two different animals, which reacted positively to skeletal muscle and to liver extract. Owing to the absence of accurate standardization, the significance of these exceptions is doubtful; but it is questionable whether any accurate standardization for this purpose is possible.

The results with the filtered extracts were similar to the others, with glycosuria slightly less. Extracts heated to 70 degrees for half an hour were negative, except for a slight glycosuria still produced by liver; here the bile or other special poisons may be thought of. The organs of the animal dead after epinephrectomy gave results identical in all respects with those from normal animals; neither increased nor diminished glycosuric effect was demonstrable.

The principal lesson from the experiments is clear, viz., that the glycosuric effect of pancreas is not specific, but is fully paralleled by that of other organs. It may also be remarked that the glycosurias resulting from the injection and from the feeding of pancreas are of radically different nature. The former is a simple toxic glycosuria, without special significance. The latter, though not specific to the pancreas, possesses the theoretical importance discussed in Chapter IX.

7. Blood and Lymph.

The latter of these may be considered first, as the briefer topic. Lepine and Barral [ref. by Kleen, p. 193] once claimed that lymph from the thoracic duct of a normal dog diminishes glycosuria when injected intravenously into a diabetic dog. Whereas Tuckett (1) observed glycosuria from injections of lymph into the portal circulation, Biedl and Offer found that prolonged glycosuria results from ligation or fistula of the thoracic duct. Thoracic duct lymph has proved useless in therapy [Falta; ref. by von Noorden (1), p. 262]. If one thing is certain on this subject, it is that the lymph is not the vehicle of the internal secretion of the pancreas, and that nothing can possibly be expected from the therapeutic use of lymph in diabetes.

Concerning the blood, much work has been done, with valuable theoretical results. Von Mering and Minkowski proved that the blood of a diabetic dog does not cause diabetes in a normal dog. Lepine [(1), p. 363] observed that a large transfusion from a normal into a diabetic dog diminishes the sugar-excretion but does not diminish the hyperglycemia. Hess (1*A*) undertook the procedure of first transfusing a diabetic into a normal dog, in the hope of stimulating the internal secretion of the pancreas, and then transfusing from this normal dog into a diabetic dog in the hope of a therapeutic result. Hess' claims of positive results were not well founded. The transfusion experiments of De Domenicis [ref. by Forschbach (1)] led to negative results. Drennan has recently performed experiments with injection of 150 cc. normal dog-blood into the veins of depancreatized dogs weighing 7–8 kilos. He concludes that intravenous injection of fresh defibrinated blood from a normal into a depancreatized dog lowers the percentage of sugar and the D/N ratio in the urine for a period of less than 24 hours. Control experiments made with injection of salt solution, stale blood, or blood

of depancreatized animals were negative. The sterile defibrinated blood loses its activity in the course of a few hours. It is therefore supposed that the action is due to the internal secretion of the pancreas, but that this is a very labile substance, quickly and easily destroyed; and that failures to secure efficient extracts may perhaps thus be accounted for.

The best and most thorough and conclusive investigation in this field is that of Hedon (7, 8, 9, 12). For establishing union between the carotid arteries, he made use of metal tubes lined with suitable pieces of fresh veins, the ends of the vein being brought out as cuffs about the ends of the metal tubes. These could then be used as easily as ordinary cannulæ, yet the blood was in contact with nothing but endothelium, and therefore did not clot even in long experiments. With admirable skill, Hedon has been able to maintain carotid cross-transfusion of pairs of dogs for as long as eight hours continuously. When a diabetic dog was thus cross-transfused with a normal dog, the glycosuria of the former was markedly diminished (*e.g.*, from 7 per cent a diminution to 2 per cent); but generally sugar appeared in the urine of the normal dog. When one dog was normal, and the other possessed a subcutaneous pancreatic remnant which was removed for the purposes of the experiment, glycosuria could be prevented from appearing during the time of transfusion. In one such experiment, a glycosuria which had already begun was completely abolished during the transfusion. Polyuria always ceased promptly with the glycosuria. Hedon wisely investigated the latter phenomenon further, and found that polyuria also ceased when two diabetic dogs were cross-transfused; *i.e.*, the change is not due to the pancreas, but is merely an injurious effect of each animal's blood upon the kidneys of the other. A curious finding was that cross-transfusion of two diabetic dogs always ends fatally. All dogs suffered serious effects from the prolonged cross-transfusion — prostration, anorexia, fever, albuminuria; some died, but the majority of normal animals recovered. Though the non-diabetic and diabetic members of a pair might both be excreting sugar during the cross-transfusion, as soon as they were separated each returned to his previous condition; the normal dog was normal, the diabetic dog was diabetic. Suitable experiments showed that dextrose or fluorescein injected in one animal passed over readily into the other, and chloralose injected in one anæsthetized also the other. The observations

of the mutual pressure and distribution of blood were also very interesting.

It is a reasonable supposition that the blood coming from the pancreas itself should be richer in internal secretion than the blood of other regions; and experiments have therefore been undertaken with the blood or serum of the pancreatico-duodenal vein. Alexander and Ehrmann found that blood from this vein, injected intravenously in depancreatized dogs in quantities of 50–150 cc., failed to influence the diabetes. In this field also, the work of Hedon has been most complete. Hedon (7) found that intravenous injection of large quantities of serum from the pancreatico-duodenal vein of a normal dog has no influence upon the glycosuria of a diabetic dog. But Hedon (13) observed that when the serum was injected into a mesenteric vein, so as to enter the portal circulation directly, the glycosuria promptly diminished almost to zero and remained low for several hours. He furthermore joined the blood-vessels of a normal and a diabetic dog in such a manner that a portion (processus uncinatus) of the pancreas of the normal animal received its arterial blood from the carotid of the diabetic animal, and so that the blood from this portion of the pancreas was drained into the jugular vein of the diabetic dog. The pancreas retained its innervation from the normal dog. There was no effect upon the glycosuria. But when the splenic artery and vein were used instead of the carotid and jugular, *i.e.*, when the blood from the normal dog's pancreas was drained directly into the portal circulation of the diabetic dog, the glycosuria fell to a very low figure and remained so for several hours. Blood-analyses showed that hyperglycemia was still present; even when glycosuria was absent, the blood still contained 0.3 per cent dextrose. Hedon concluded that the blood of the pancreatico-duodenal vein contains an active pancreatic secretion, but that this can exert its influence only when it enters directly into the portal circulation; and that the first effect is not upon the hyperglycemia but upon the glycosuria, *i.e.*, the permeability of the kidney is altered.

As previously noticed, Hedon's latest work (14) is not so clearly explainable on the basis of internal secretion, and he attributes the earlier results with carotid cross-transfusion to the simple toxicity of the foreign blood. The theoretical bearings were discussed in Chapters VII and XVI. The possibility that it may be necessary for the internal secretion of the

pancreas to enter the portal circulation, will be considered in Chapter XX.

Mention may be made here of two transfusions (not crossed) performed in animals with diabetes gravis. One was Dog 49 on June 2. The other was Dog 184 (see protocol) on February 18. In each case, the diabetic animal was so weak that it was expected to die over-night [but still excreting sugar. Cachexia does not cure diabetes.] The trouble with Dog 49 was distemper and diabetic cachexia. Dog 184 was in good condition except for having been starved to the verge of death. Each received a direct transfusion (carotid into jugular) from a normal dog about twice its own size, till the normal dog was practically pulseless. Immediately after the transfusion no benefit was apparent; the weakness was even greater than before, perhaps from the simple strain of operation. But by the next day, the benefit to the general strength was evident. Dog 49 was strengthened so that a large subcutaneous injection of dextrose ($12\frac{1}{2}$ g. per kilo) was endured on June 3, and death did not occur till the afternoon of June 4. Dog 184, which had seemed so far gone that feeding would probably not have saved life, was able to endure one additional day of starvation, and then was saved by feeding. There was not the slightest beneficial effect upon the glycosuria in either case.

I regret that circumstances did not permit undertaking cross-transfusions by Hedon's method. But it seems reasonably certain that transfusions in the type of dogs which I have studied will be as negative as Hedon found them to be in completely depancreatized animals. This type of dogs possess some advantages over the completely depancreatized ones. For one thing, Hedon found cross-transfusion of completely depancreatized dogs to be fatal; but this will probably prove to be connected with the typical cachexia; and with the partially depancreatized animals it is to be expected that cross-transfusion will be feasible. One of the interesting experimental possibilities is cross-transfusion between a dog with diabetes gravis (or a completely depancreatized dog) and one with diabetes levis. If the latter loses amboceptor to the former, there might be found a perceptible aggravation of the diabetes in the latter.

For purposes of diabetic therapy, it may be concluded that transfusion stands on the same plane as in other conditions. It

may be of service in strengthening a patient temporarily for some operation or other ordeal. It will not benefit the diabetes.

8. Parabiosis.

Medical attention was first directed to this fascinating subject by the announcement published by Sauerbruch and Heyde in 1908. These authors review the previous literature. They trace briefly the development of plastic surgery, beginning with the plastic restoration of the nose, first performed by the Italian surgeon Tagliacozza, who in 1597 formed a nose from the tissue of the arm; the so-called "Indian method" and other procedures later came into use for this purpose. Aldovandi in 1793 transplanted the spur of a cock to the animal's comb, and Hunter and Baronio performed similar experiments. Portions of skin were also transplanted from one part of an animal's body to another part. Then came the operations for the covering of areas denuded of skin, culminating in the method of Thiersch. Similar methods were applied to mucous membranes, and finally were performed transplantations of cartilage, bone, blood-vessels, and entire organs.

The starting-point for a different application of these methods was the work of P. Bert in 1863, who united pairs of rats by means of bridges of skin. Later v. Eiselsberg had joined rabbits temporarily, for obtaining healing of a flap from one thrown over to cover a skin-defect of the other. With lower forms of life, zoölogists had succeeded in more radical experiments. Born had succeeded in uniting different parts of the bodies of frog-larvæ in different ways. Korschelt had taken the head-end of one earthworm and the tail-end of another and joined them to make a new animal. All the above references are from Sauerbruch and Heyde; but mention should not be omitted of the experiments of Harrison, whose remarkable grafting of tadpoles furnished a brilliant contribution to the study of the development of the nervous system.

Sauerbruch and Heyde attempted an analogous union of mammals. Rabbits were employed, and the best method was found to be an anastomosis of the peritoneal cavities. A suitable opening was made in the side of each animal, and the parieties of each sutured layer by layer to the corresponding structures of the other. To the Siamese-twin existence thus brought about was given the name of parabiosis. For successful union, the

authors found it necessary to use young animals of the same sex and the same litter; under other conditions the lines of junction broke down and the experiments failed. Other authors have found these requirements not indispensable, but the conditions named are nevertheless the most favorable. Sauerbruch and Heyde thought they could demonstrate in microscopic sections a direct union of the blood-vessels of one animal with those of the other. They proved that potassium iodide or sodium salicylate, injected subcutaneously in one animal, appears in the urine of both. Strychnin injected in one poisoned also the other. Also, infection of one member of the pair with anthrax resulted in death of both, with the usual swarms of bacilli in the blood of both. When a stronger and a weaker animal were united parabiotically, the stronger seemed to live at the expense of the weaker, the former thriving, the latter wasting away. When one member of a pair died from any accidental cause, the death of the other followed generally within 3 or 4 hours, sometimes as early as ½ hour, presumably from toxic absorption. By separating the living animal from the dead one within half an hour its life could be saved. When both kidneys were removed from one member of a pair, death resulted in this animal, though the other also showed uremic symptoms. In one experiment, a crossed anastomosis of the large intestines of the two animals was made, the contents of the upper intestine of one thus flowing into the lower intestine of the other, and vice versa. The pair lived in health under these conditions for 19 days.

These striking experiments attracted the attention they deserved; the method has been used for a variety of biological studies, and has given rise to a literature which cannot be completely reviewed here. Rabbits, rats and mice have been the animals especially used. A few successes have been obtained with dogs, but they fall far short of the other species named in the ease with which they form or endure such union. Hedon and numerous others have met with failure.

In the work of Amantea and Manetta, and of practically all the other writers to be named here, is found confirmation of the fact that soluble substances (iodides, salicylates, lactose, methylene blue, etc.), injected in one animal pass into the urine of the other. The actual quantity excreted is greater in the animal which receives the injection. The fact of the passage of substances of this character from one to the other animal could be explained

by either lymph- or blood-conveyance. The most important objects of later study have been whether an actual union of blood-vessels and circulation occurs, and whether substances of larger molecule, *e.g.*, anti-bodies and internal secretions, pass from one animal to the other.

The question of blood-vascular union has been definitely decided in the negative. Ranzi and Ehrlich, who studied especially the effects of toxins and the formation of anti-bodies in parabiotic animals, proved that a colored injection mass injected into the aorta of one animal stops accurately at the line of union. Morpurgo made the same demonstration in mice, the completeness of whose union had been proved by the fact that one was living without kidneys; nevertheless the injected gelatin mass failed to pass the line of union. Cristea and Denk made an ingenious contribution to the proof by taking advantage of the peculiarities of hirudin, viz., that this substance produces incoagulability of the blood when injected intravenously but not when administered subcutaneously or otherwise. Cristea and Denk therefore united rabbits in parabiosis, and after union was complete, injected hirudin intravenously in one animal and studied the coagulation-time of the blood of each. The result was incoagulability of the blood of the injected animal, and no effect upon the other. They accordingly concluded that there is no blood-communication between animals living in parabiosis.

Removal of viscera has been a favorite mode of experiment for the question whether metabolic substances may pass from one parabiotic animal to its partner. Though Sauerbruch and Heyde found nephrectomy fatal in rabbits, it has since then frequently been performed in rats and mice with survival. Morpurgo's mice lived for long periods with both kidneys removed from one member of the pair. Yet if only one kidney was removed from one of the animals, the resulting hypertrophy was limited to the remaining kidney of this animal; it did not affect the kidneys of the other. Birkelbach has reported more recently a series of such experiments in rats and mice. He confirmed and extended Morpurgo's observations of toxic phenomena under these conditions. Although it can be demonstrated that the kidneys of the one animal perform the full excretory function for the two, yet the gradual development of ascites, congestion of the liver, hypertrophy of the kidneys and heart, and general disturbance of nutrition led ultimately to death. The author interprets the

phenomena as due to deficiency of a renal internal secretion. Possibly a little suggestiveness on this point may be contained in those experiments of Morpurgo which showed renal hypertrophy limited to one animal.

Lombroso has made interesting contributions to this question. Lombroso and Bolaffio proved that in parabiotic female rats and rabbits, the breasts of the virgin member of the pair were not affected by pregnancy or lactation in the other animal; and of two pregnant parabiotic females, each could produce her young at her own time without influencing or being influenced by the pregnancy of the other. In this paper, the literature of the hormone-origin of labor and lactation is reviewed. Lombroso (17) analyzes the preceding experiments as denoting one of two things; either hormones for the functions studied do not exist, or these hormones are unable to pass the line of union between the two animals. He then proceeded to show that if one parabiotic rat is starved while its partner is full-fed, the starved animal dies fully as soon as a normal control; that is, food substances do not pass from the fed to the starved member of a pair. Of two male rats in parabiosis, both testes were removed from one, and it in due time showed sluggishness, obesity, and the other usual effects of castration, while its companion remained normal. If both adrenals were removed from a parabiote, it was found to die in 3–12 days, while the survival of controls never exceeded 5 days; but rats vary so in this respect that the author prefers to draw no conclusions. Lombroso's conclusion is that though freely soluble substances such as the urinary constituents may pass freely from one parabiote to its partner, the more complex bodies such as food-materials and internal secretions cross the line of union only to very slight extent.

In view of the experiments of Schwarz, parabiosis would be interesting between a normal rat and one which has survived removal of both adrenals. The question would be whether the liver of the latter regains its glycogen content. The question of the passage of an adrenal secretion from one to the other might thus be illuminated a little. It may also be noted in passing that cancer experiments in parabiotic animals are robbed of their significance by these researches of Lombroso. The failure of an immune to protect its non-immune partner does not disprove the existence of protective substances, but may mean merely the inability of these substances to pass the line of union.

The one notable application of this method to diabetes was made by Forschbach (1). This investigator not only succeeded in uniting dogs in parabiosis, but succeeded also in joining those of the same litter but different sexes, and in one instance united successfully two adult dogs of different sex and breed. He confirmed Sauerbruch and Heyde's observation that when animals of unequal strength are thus joined, the weaker one is liable to die of a rapid cachexia. In applying the method to diabetes, Forschbach's procedure was to wait till union was complete, as proved by passage of injected substances, then to subject one member of the pair to total pancreatectomy. The most successful experiment was with two puppies; after pancreatectomy in one, neither excreted sugar for 40 hours; then glycosuria began in both, varying from 0.1 to 0.4 per cent. Polyuria was absent, even when the depancreatized animal was fed 4 g. dextrose; of this quantity, only 0.55 g. was excreted. On the fourth day after pancreatectomy the two animals were separated by operation. The normal animal survived; the diabetic promptly showed peritonitis. In the latter, the glycosuria rose only to 1 per cent, doubtless on account of weakness; but the quantity of sugar excreted in the 22 hours of life was greater than in the previous $3\frac{1}{2}$ days. In another experiment, two adult dogs of different sex and breed were successfully united, and the pancreas later removed from one. The first urine following operation seemed to indicate full diabetes, for it contained 4.8 per cent sugar. Glycosuria rapidly diminished, and the D/N ratio, wound-healing, and general behavior of the operated animal corresponded to a very mild diabetes. Both of the animals were on meat diet. The urine of the normal member of the pair was sugar-free throughout. The animals lived till the seventh day after pancreatectomy, when breaking down of one angle of the junction necessitated killing them.

Pflüger (23) misinterpreted Forschbach's findings, by alleging that the puppy-experiment proved that *both* animals became diabetic. In his complete publication, Forschbach was able to answer this objection based on his preliminary announcement. Traces of glycosuria are nothing very remarkable in dogs subjected to any condition of slight intoxication. When sugar is injected in one animal of a pair, it excretes more than its partner. When Forschbach fed dextrose to one of these puppies, the resulting increase of excretion was exclusively confined to it. The

assumption of a simple passage of sugar from the depancreatized to the normal animal therefore fails to explain the relative equality of the glycosuria; especially on one day (May 6) the urine of the normal puppy contained 0.35 per cent dextrose, while that of the depancreatized puppy showed only a doubtful trace. The most convincing feature is the wound-healing. Since hyperglycemia is not the cause of the defective wound-healing in depancreatized dogs, it seems impossible to explain the successful healing in Forschbach's experiments except on the assumption of a transfer of internal secretion.

Experiments with parabiosis were a feature which I had earnestly desired to carry out, because of the unique opportunities afforded by the type of diabetes; but circumstances again prevented. The work went no farther than a few preliminary experiments. In order to learn the technique, distempered animals were used; and on the chance of benefiting the distemper, the sick were united with immune animals, some of them recently recovered from the disease. Five such pairs were made. Close apposition was maintained by the following means. Some hours before operation, the two dogs were made to stand close together in the desired position, and a strong wooden crate was made to fit them exactly. A partial partition of thin wood extending inward from the front kept their heads separate. Supports were then built in for each animal's belly and head. At the close of the operation, a strong canvas binder was placed about the bodies of both dogs; they were then transferred to their crate. The open structure of the crate afforded plenty of air. The height of the supports was such as scarcely to touch the animal's bellies; they stood on their feet when they chose; at other times they rested on the supports; there was no appearance of any great discomfort, and a surviving animal was always vigorous and frisky when removed from the crate.

The unexpected outcome is worth noting. Every distempered animal died within 24 hours; every one of the normal animals paired with them survived in excellent condition. Some of the distempered animals were at such early stages of the disease, with so much strength remaining, that the sickness, operative shock, etc., seem insufficient to explain the contrast with the immune animals. In one case a distempered animal was found dead in the morning; the time of death was uncertain, but rigor was complete. It was separated from the living partner with

aseptic care; a loop of the latter's intestine was found in the dead dog's peritoneum; but the living animal was in excellent condition and recovered uneventfully. The failure to benefit distemper accords with my experience with transfusions. Blood from immune animals at various periods during and after convalescence, whether given as serum or defibrinated blood, or by direct transfusion, has had no effect upon distemper, aside from the transitory stimulation which is the rule after transfusion.

Since pregnancy resembles parabiosis, advantage was taken of one opportunity to perform an experiment analogous to those of Carlson and Drennan. In a pregnant animal near term, nine-tenths of the pancreas was removed. Instead of the usual diabetes gravis, there was not a trace of glycosuria. Furthermore, the dog ate bread-and-meat mixture, also milk, and moderate (unmeasured) quantities of glucose were added to this diet, all without glycosuria. Death occurred seven days after operation, from undetermined causes; there was no visible sign of infection, but the temperature, which had been normal, rose on the day before death to 102^{7}.

Dogs with the type of diabetes described in Chapter X obviously open up new opportunities for the application of parabiosis to diabetes. Along with a severe and uniform diabetes, such dogs have a general strength and resistance resembling the normal. It is thus possible to make tests in two directions.

A. *The Cure of Diabetes.* — Instead of joining the animals first, and later performing pancreatectomy, it is possible to allow a dog to be diabetic for weeks or months, and to test it by metabolism experiments, and it is still in condition for the parabiosis operation. The actual cure of diabetes under these conditions would be rather clear evidence in favor of an internal pancreatic secretion, and would open up the question why parabiosis may prevent diabetes, whereas cross-transfusion does not.

B. *The Production of Diabetes.* — If an animal not quite diabetic, or with diabetes levis, is joined in parabiosis with a severely diabetic animal, there would seem to be a chance for the production or aggravation of diabetes in the former animal. The important point of producing diabetes by demonstrably *functional* means would thus be touched. The question whether a diabetes thus produced would continue after separation of the animals is less doubtful; if diabetes can be produced and maintained for a sufficient length of time by any means

whatever, it will persist, just as it does in human patients after trauma, etc.

Other possibilities are numerous. For example, as suggested in Chapter X, it may perhaps be possible by the method there described to produce diabetes in rabbits, frogs, or some other species better suited for parabiosis than dogs. Also, though difficult, it would seem not impossible that the processus uncinatus of one animal's pancreas might be transplanted, with a pedicle, into the spleen or other suitable organ of its diabetic partner, and the functional result demonstrated by subsequent separation of the animals.

An experimental cure of diabetes by parabiosis, even if obtained, is not likely to find any practical application to human patients. From a speculative standpoint it is possible to think of patients with different diseases joined in this manner, the sound organ of one functionating for the diseased organ of the other, and vice versa. Experimentally, there is a bare chance that such a condition may be realized; for example, a diabetic animal joined with one which has lost its thyroid, parathyroids, or hypophysis. But practically, in addition to all other considerations, the mutual injury of two animals joined in this manner must be remembered, and the special and fatal injury which befalls the weaker of the pair. Contributions to the theory are therefore what we should expect from parabiosis.

9. Grafts.

Since a small portion of pancreas is able to prevent diabetes, and since so many other organs have been transplanted with success, the attempt to treat diabetes by means of grafts of pancreatic tissue must be considered among the possibilities. It is instructive first to review the results with other organs.

The greatest success has attended transplantations of the thyroid and parathyroids. The following references in this paragraph are taken from Biedl (3). Schiff was first in this field, and in 1884 succeeded in keeping thyroidectomized dogs alive by means of intraperitoneal thyroid grafts. Next v. Eiselsberg proved more definitely that the implanted thyroid can actually survive and grow. Kocher performed successful transplantations in human patients with myxœdema, and Bircher obtained transient improvement by this method. Victor Horsley then advised transplantation of sheep thyroid into human patients, and various

surgeons reported more or less temporary benefit from the operation. A long list of investigators (see Biedl) then made grafts in various animal species under varied operative conditions, mostly with positive results. The subcutaneous or preperitoneal tissues were the favorite sites; but Kocher recommended the epiphyseal ends of bones, and Payr's example of implantation into the spleen has been widely adopted. By following the histologic changes, it was learned that the grafts at first show degenerative processes, which in the center may amount to actual necrosis. The periphery of the graft survives because better nourished; vessels grow into it here, the thyroid tissue hypertrophies, and later the graft is found composed of flourishing cells about the periphery, and a small central scar representing the necrotic area. Cristiani showed, and was confirmed by Salzer, that in thyroidectomized rats the graft takes root and grows far more promptly and actively than in normal animals; the interpretation is that conditions for the growth of the thyroid cells are more favorable in animals lacking thyroid tissue. Grafts of this sort in thryoidectomized animals are completely successful for function, and Payr has reported marked benefit from implantation of a piece of thyroid into the spleen, in a myxœdematous child which had failed to improve on thyroid feeding. The method seems feasible in those cases of hypothyroidism which resist the usual organotherapy.

With parathyroid transplants a similar success has been achieved. [References in this paragraph from Biedl (3).] Biedl planted the external parathyroids of cats and dogs into the spleen, where they preserved their function in such manner that the thyroid with the internal parathyroids could be removed without symptoms. Successful parathyroid grafts in various parts of the body in various animal species were obtained by Pfeiffer and Meyer, Hermann and Harvey, Walbaum, Cristiani, Camus, and Leischner. Success has attended iso- as well as auto-transplantations. Cristiani, in particular, in a series including hundreds of thyroid and parathyroid grafts, proved that the latter show at first a slight tendency to central necrosis, but soon recover their normal structure, and may be found unchanged in rats after 2 and in cats after 5 years. The functional as well as the anatomical success is perfect. Likewise in a human patient, v. Eiselsberg implanted in the Rectus abdominis one parathyroid obtained from another patient; a practically complete cure of the existing tetany was the result.

A review and bibliography of this subject will be found in the paper of Pool. It contains a report of a post-operative case of tetany treated by transplantation and Beebe's nucleoproteids. The latest article to my knowledge is that of Halsted, a report of a dog maintained in good health by a parathyroid auto-graft approximately one-fourth of a millimetre in diameter. Halsted considers functional results possible even from tiny grafts of thyroid and parathyroid; and believes that the chance of a successful graft is immensely increased in cases where parathyroid deficiency exists.

The greatest difficulty of all has been experienced in connection with the adrenal medulla. This is what we should expect, in view of the embryonic relationship of chromaffin tissue with nerve-tissue. The following authors have met with failure [references in this paragraph from Biedl (3)]. Canalis in 1887 implanted bits of adrenal in the kidney, but they underwent necrosis. Abelous, Abelous and Langlois, and later Gourfein attempted transplantations in frogs unsuccessfully. Boinet transplanted adrenals intraperitoneally in rats and saw them more or less rapidly absorbed. Jabulay is said to have transplanted adrenals from dogs into two human patients with Addison's disease; in each case death occurred within 24 hours. Hultgren and Andersson made three unsuccessful implantations in cats. Poll transplanted adrenals under the skin or into the back-muscles of rats, and followed the histologic changes. Central necrosis occurred, involving not only the medulla but also the inner layers of the cortex. The remaining outer portion of the cortical tissue also undergoes extreme regressive changes, but by the third week regeneration begins, and the normal structure of cortical tissue reappears. Cristiani also observed destruction of medullary tissue and preservation of cortical tissue in his experiments with rats. Stilling showed that adrenals transplanted into the testes in rabbits show typical cortical tissue after $1\frac{1}{2}$ to 3 years. Imbert met complete failure in transplanting adrenals of dogs into the kidneys. Strehl and Weiss made implantations into pockets between musculature and peritoneum, also into the liver and kidney; but the grafts either of whole or of portions of adrenals quickly disappeared. Schmieden obtained partial success in transplanting portions of rabbit adrenals into the kidneys, but concluded that the life of the grafts could not exceed a year. Transplantations into the spleen by Coenen, Kreidl, and Biedl,

all met with a similar transient success; the grafts were not permanent.

Moussu and Le Play (2), working with dogs and rabbits, failed to obtain functional grafts in the spleen. The cortex was found to persist a short time, but the medulla quickly suffered necrosis, and the animals died as soon as the other adrenal was removed. Shiota found that adrenal tissue transplanted into the spleen or kidney loses its adrenalin within 48 hours; sooner in the spleen than in the kidney, and sooner in a small than in a large graft. The real formation of adrenalin ceases immediately and permanently at the time the graft is made. The cortex was found present in excellent condition after as long as 17 weeks.

The first authors to report complete success with adrenal grafts, and the only ones who have claimed such success by grafting without a pedicle, were Busch and Van Bergen. Their records show several successful grafts of adrenal tissue of rabbits into the kidney, with preservation of medullary as well as cortical tissue. The authors apply strict criticism to their functional results, and claim only one objection-free result. In this experiment, a rabbit's left adrenal was removed and a portion grafted as usual into the kidney; 102 days later the right adrenal was removed; after another 62 days the kidney containing the adrenal graft was removed, and the rabbit died $3\frac{1}{2}$ days later with signs of adrenal insufficiency. The transplanted adrenal tissue was found preserved, both medulla and cortex; and no other adrenal tissue was revealed by the autopsy.

The most extensive experiments in this direction with successful result are those of v. Haberer and Stoerk [see also Stoerk and v. Haberer]. Their method was to swing the adrenal, attached to its pedicle, into the kidney. Anatomical and functional success, as respects both cortex and medulla, was obtained in 50 per cent of the cases. An exceedingly pronounced and prolonged interaction of retrogressive and regenerative changes resulted from the implantation. Frequently all the tissue underwent necrosis except that immediately surrounding the pedicle; this living tissue hypertrophied, degenerated, and regenerated successively, till after some five months a practically new adrenal was the result. This consisted of both cortical and medullary tissue; the former pedicle was completely atrophied, and the graft was vascularized from the surrounding renal tissue. In successful cases this graft was able to preserve the animal's life after removal

of the second adrenal. In a second series of 11 animals, the procedure was in a first operation to transplant one adrenal into the corresponding kidney, in a second operation to transplant the other adrenal into the other kidney, and in a third operation to remove one kidney with its contained adrenal. Six of these animals died after the third operation; five survived permanently. Haberer and Stoerk's experiments also yielded the interesting information that loss of one adrenal does not affect the course of events when the second adrenal is transplanted; the same degenerative processes occur as above described. But in experiments where first one adrenal is transplanted and then the other adrenal removed, the chance of survival is increased if the interval between the operations is relatively short (11–14 days). Biedl obtains the impression that removal of the second adrenal at just the right stage serves to stimulate the regenerative processes in the graft.

The opinion of Biedl, that the history of adrenal grafts holds out promise of a surgical treatment of Addison's disease, cannot be shared unless the method of Busch and Van Bergen proves feasible. The pedicle method of Haberer and Stoerk is not applicable to anything but auto-grafts, and thus loses practically all therapeutic significance. One bare chance is possibly open. Since implantation seems to constitute such a powerful stimulus to an adrenal, it might possibly be that in an early case of Addison's disease, if tubercular or other factors do not prevent, an adrenal on its pedicle might be implanted in the kidney, in the hope that the increased blood-supply and general stimulus might excite it to efficient hypertrophy. Obviously, the chance is not great, especially since Addison's disease is supposed to involve the whole chromaffin system; but it might possibly be worth a surgeon's while to try.

After reviewing the numerous attempts at transplantation of other organs, one is surprised, on coming to the pancreas, to find how little has been done. The general outcome has been more encouraging than with the adrenal, for example, and yet investigators have seemed to show a disinclination to touch the pancreas. It is part of the general hopelessness that has settled down upon the whole subject of diabetes.

The processus uncinatus brought out under the skin in the customary way is not truly a graft, though commonly referred to by that name. The procedure is a mere dislocation of a portion of the pancreas. But mention has already been made of

experiments of Thiroloix, Hedon, and Lombroso, in which the pedicle of the subcutaneous gland-fragment was cut; under these conditions it becomes a true graft, and the absence of diabetes characterizes the experiment as a successful transplantation of the pancreas. The claims of success by grafting without a pedicle, by Thiroloix (4) and by Martina, were also mentioned in Chapter VII.

A number of clinical attempts to treat diabetes by means of grafting have ended uniformly in failure. Williams tried transplantation of sheep pancreas into man, but naturally observed no benefit. I have not followed the other early clinical literature. No recent attempts have been made.

Ottolenghi in 1901 made many temporarily successful grafts from one guinea-pig to another. Pieces were taken, from a pin-head to a pea in size, and transplanted generally into the peritoneum, sometimes into the spleen or liver, or subcutaneously. Within 24–48 hours the central portion showed beginning necrosis; next to it was a zone where fat-droplets were numerous. The border-zone of the graft showed karyokinetic figures and proliferation, but never formation of new acini. As days went on, small cysts were found, formed by distention of small ducts or acini, and lined with flattened epithelium. Normal-appearing acini were mingled with them. The islets apparently disappeared early by a process of rapid necrosis.

Pflüger (13) referred to Nussbaum's discovery that a piece of frog-testis will perform its internal function when transplanted into a castrated frog. Pflüger tried to imitate this procedure with the pancreas, inserting it under the skin or into the peritoneum; but he found that even four entire glands thus transplanted into a depancreatized frog had no effect upon the glycosuria. The result may be accepted as correct chiefly on the basis of other work; Pflüger's own experiments are open to some question because his frogs were ordinarily kept on ice and a glycosuria might therefore be due to cold.

Kyrle in 1908 used a well-planned method, in that he imbedded in the spleen a portion of pancreatic tissue with its original vascular supply preserved. Some time later, in a secondary operation, the pedicle was cut, and the graft lived without difficulty. Kyrle's work was entirely anatomical; the remainder of the pancreas was not removed and no effort was made to demonstrate the function of the graft. The longest experiment was

40 days. He described the regenerative processes which were active in the transplanted tissue; but in such a graft, atrophy was much more rapid than in a similar portion of tissue separated from its duct and left in its natural position.

Tiberti (3) in 1909 tried grafting bits of pancreas of rabbits and guinea-pigs into the liver and spleen. After two days, the centers were found necrotic, but in the peripheral zone both the acini and islets were distinct. In later periods, groups of cells were discoverable which might doubtfully be interpreted as islets; but one gains the impression that the life of these grafts was very short.

The only instance of successful pancreatic grafting, demonstrated both anatomically and functionally, and also the longest known survival of a pancreatic graft, is that of Pratt and Murphy, by the pedicle method, as mentioned in Chapter VII. The questions are so interesting, and the method so feasible, that it is pleasing to know that further experiments will be forthcoming. Also, in dogs such as described in Chapter X, it might be possible to attempt not only the prevention but also the cure of diabetes by means of grafts.

In general, we may conclude that deplorably little has been undertaken with grafts of the pancreas, in comparison with the extensive researches with transplantation of other organs. In proportion to the number of attempts, the successful examples of pancreatic grafting are very encouraging; the results fall short of those with the thyroid or parathyroid, but equal or surpass those with the adrenals. Much theoretical interest still attaches to transplantation experiments. Clinically, the method will probably never find application, unless some entirely new principle of organ-transplantation shall first be discovered. With present knowledge and methods, transference of pancreatic tissue from one individual to another is inevitably difficult and uncertain; the grafts are small, and their life is short. Small portions of normal pancreatic tissue left in their normal location with normal blood-supply invariably atrophy and give rise to diabetes within a few months; and whatever results follow experimental autografts, we cannot expect iso-grafts to maintain function for more than a brief period at the best. These objections, combined with the injury and danger of operations in diabetic patients, probably exclude the grafting method from therapeutic availability in diabetes.

10. Operations upon the Nervous System.

No state of the nervous system can prevent diabetes when the pancreas is absent. As previously mentioned, the findings of Chauveau and Kaufmann with section of the spinal cord represented nothing but a simple suppression of the glycosuria. In human diabetes, however, we are dealing generally with a condition in which the pancreas is present and relatively unchanged in appearance. If it is found that this pancreas — initially at any rate — is anatomically sound, and that the functional impairment is due to a disturbance of its nervous control, obviously the entire therapeutic view-point undergoes a revolution. Hopelessness is at once replaced by hope. Such a nervous disorder must be one of two things; it must be (A) paralytic or (B) irritative.

(A) If the loss of the internal secretory function of the pancreas is a paralysis of nervous origin, analogous to a muscular paralysis of similar origin, it should be subject to treatment on the same basis as the muscular paralysis. A muscular paralysis may be cured by nerve-grafting. There is hope that a glandular paralysis may be cured in the same manner. Attention may be called to the paper of Erlanger, "On the union of a spinal nerve with the vagus nerve." The interesting results there described augur well for future investigations in this field. There is a certain problem in determining what is the best and easiest site for grafting in a fresh nerve-supply to the pancreas. The nerve-roots and the splanchnic nerves are entitled to consideration, but naturally the most obvious place is in the nerves which directly supply the gland. Any healthy nerve except a pure afferent nerve is presumably at the surgeon's disposal; the whole splanchnic system is under suspicion as to its soundness in diabetes, so the choice will probably fall upon either the vagus or some nerve supplying voluntary muscle. When pancreas-tissue is transplanted into the spleen or under the skin and the pedicle cut, a fresh nerve-supply is obtained; for example, in the microscopic specimens from Pratt and Murphy's dog, numerous non-medullated nerve-fibres are seen entering the graft. Such fibres, subserving vasomotor or other functions, are apparently able to innervate the pancreatic cells or enter into suitable communication with the intra-pancreatic ganglia. The problem is the purely technical one of grafting healthy nerves upon the various trunks which pass to the pancreas. In the present state of the art, surgeons will not be baffled by a technical problem of this nature.

(B) If the disturbance of the pancreas is irritative, a cure may consist either in destroying the abnormal nerve-supply, or, in addition, grafting in a healthy nerve-supply. Here again, the seat of disturbance is of some importance; we may think of the central nervous system, the semilunar ganglia and neighboring cell-stations, or the resident ganglia of the pancreas. An efficient check to the disturbance might therefore be obtainable from cutting of nerve-roots or of the splanchnic nerves, or from extirpation of the semilunar ganglia or of their branches to the pancreas. A vagus nerve might be ingrafted into a splanchnic, or other nerves suitably anastomosed in other locations. The first condition for which it seems desirable to call serious attention to this mode of treatment is traumatic diabetes. Here generally it is reasonably certain that a central nervous injury gives rise to the disturbance. There are good grounds for believing that this disturbance is transmitted along the splanchnic nerves. It is therefore proper to invite consideration of the proposal that in suitable cases the splanchnic or other nerves should be cut. There is here the question as to the real seat of irritation. Does the disturbance consist in a continuous stream of irritation passing out from the injured cranial centers? Or does the original shock, transmitted by the splanchnics, throw the abdominal sympathetic suddenly out of gear so that the local ganglia remain in a condition of chronic irritability without further stimulation from above? Or again, does the continuance of abnormal stimulation from the higher centres *gradually* unbalance the abdominal sympathetic, so that a "diabetic habit" is formed in these centres? Decision as to which of these possibilities is correct will decide the therapeutic indications. If the first view is correct, then section of the splanchnic nerves, by stopping the stream of irritation, should result in cure of the diabetes. If the second possibility is correct, extirpation of the semilunar ganglia or of their branches to the pancreas might stop the diabetes, or the irritable condition might involve the intra-pancreatic ganglia which are beyond operative interference. Under ordinary conditions, it would be desirable to wait a certain time in order to see if the diabetes tends to clear up of itself. But if the third suggestion is correct, the longer the diabetes persists the less would be the chance of checking it, and operation at the earliest possible moment would be advisable. At present it can only be said that the first possibility is most probable; the higher nervous centres are the ones that have been

injured, and the irritation most probably proceeds from them. In this case, cutting of the splanchnics is indicated. It may be urged in favor of the operation that it has been proved harmless in animal experiments, and that if desired the nerves can be sutured at the same operation at which they are cut; for by the time the fibres regenerate the acute disturbance will presumably be over. The risk is sufficiently small, and the theoretical indications sufficiently strong, that it would seem that a surgeon might be justified in making such an attempt, rather than sit idly by and see his patient slip steadily down-hill into a hopeless diabetes. Incidentally, since he will be working in the neighborhood of the pancreas and since diabetes never follows division of the pancreatic nerves, he might increase the chance of success by severing the nerves accompanying the principal vessels to the pancreas, thus providing against the contingency of a cœliac location of the irritation.

Diabetic animals offer only limited opportunity for experiments concerning this question. In animals, such as Dog 63, it may perhaps be tested whether splanchnicotomy or other operative procedures may *prevent* diabetes following a central nervous injury, and we have some reason to expect that such prevention will be possible. Some of my experiments may perhaps indicate that "enervation" of the pancreas-remnant has a similar prophylactic influence. If a successful method is devised, whereby a considerable proportion of dogs can be made diabetic in a manner analogous to Dog 63, it may be feasible to attempt to cure the diabetes by suitable cutting of nerves within the first days following the piqûre or analogous lesion. Such experiments would be of preëminent value in connection with the possible surgical treatment of traumatic diabetes. But unless performed early, a cure in these dogs will probably be impossible, owing to the relatively early onset of organic changes in the pancreas. The possibilities of nerve-section in dogs are thus limited, though results if successful must be of the highest value. Nerve-grafting in dogs is essentially hopeless. Long before the new fibres could reach their destination, the specific anatomical changes in the pancreas have reached a stage which is presumably beyond hope of repair. The changes in question are so much more rapid and extensive in dogs than in the average human patients, that the time-element, if nothing more, precludes in dogs the success which may perhaps be obtainable in human patients.

For this reason the experiments in nerve-grafting, which were in my mind at first in connection with diabetes in dogs, were not undertaken. The following was devised as a partial substitute. In case a pancreatic graft is made, nerves grow into it from the surrounding tissues, along with blood-vessels. If a dog has diabetes, the attempt may conceivably be worth while to place his pancreas-remnant where it can obtain an additional nerve-supply and incidentally blood-supply, a procedure somewhat similar to the Edebohls operation upon the kidney. It may then be observed whether the pancreas-remnant recovers any of its lost function under these conditions.

Dog 155 (see protocol) was favorable for the purpose because diabetes resulted with an unusually large pancreas-remnant; theoretically the chances of recovery of function should therefore be at their best. As soon as it was certain that the diabetes was permanent (December 5), the pancreas-remnant was brought forward so that its lateral surfaces were in contact with tissues of the abdominal wall, as in the case of a subcutaneous graft. The protocol shows that the diabetes remained unchanged. On December 23 this experiment was interrupted and the dog used for another purpose. The criticism may be made that the time between December 5 and December 23 is not sufficient for observation of the effects of ingrowth of vessels and nerves. The only answer is that the dog by December 23 was growing seriously weak, and death would soon have put an end to the experiment in any event.

An unintentional experiment of this type was performed in Dog 146. The dog was made diabetic by operation on November 11. On December 2 the abdomen was opened for another purpose, and it was found that omental covering of the remnant had been forgotten or unsuccessful in the first operation. The pancreas-remnant was found imbedded in a dense mass of stomach, intestine and liver. Firm adhesions, bleeding freely, bound the remnant on all sides to these viscera. Nevertheless the diabetes had been fully as severe as ordinary. I am therefore convinced that this class of experiments is profitless. At best, the ingrowth of vessels and nerves is too slow and too slight, and the pancreatic changes too rapid. The only experimental prospect therefore seems to be in the prevention or early checking of diabetes in animals of the type of Dog 63, by simple section rather than grafting of nerves.

My experiments have been continued in other directions, for which dogs are suitable. Whatever these other experiments may lead to, the possibility remains that diabetes may be curable by appropriate nerve-operations, and that this may yet prove itself the method of choice. It is to be hoped that the laboratory will soon yield further evidence showing that diabetes is ordinarily a disease of the nervous system. It is to be hoped that clinicians will make use of this knowledge as a basis for careful surgical experiments. The disease in question is hopeless. The operative procedures involve practically nothing but the risk of a simple laparotomy. Failure should be harmless, and success means much. Possibly more light from animal experiment should be awaited before venturing far with human patients. But if it be once reasonably established that diabetes is a nervous disease, then there is much attractiveness in the idea of undertaking to cure it by giving the pancreas a new nerve-supply.

CHAPTER XIX.

THE POLYGLANDULAR DOCTRINE.

A CERTAIN degree of inter-action and inter-dependence between the different organs of the body is self-evident. This principle has in recent years been raised to capital importance in an attempted explanation of different metabolic abnormalities, especially diabetes mellitus. The pancreatic diabetes discovered by v. Mering and Minkowski was found to differ in important particulars from the clinical disease in man. Also, the search for demonstrable lesions of the pancreas in human diabetes has not met with success sufficient to satisfy many students of the disease. On various clinical and experimental grounds, the belief in pancreatic disorder as the essential, sole and invariable cause of diabetes has come to be denied or doubted by numerous writers. One school has set up the hypothesis that diabetes consists in a loss of balance between antagonistic glands of internal secretion.

This doctrine of polyglandism or "Wechselwirkung" was brought into prominence especially by Eppinger, Falta and Rudinger in 1908. These authors obtained experimental results as follows. Thyroidectomy reduces the fasting nitrogen excretion of dogs to about half the normal, and feeding of fat or carbohydrate reduces this nitrogen excretion very slightly if at all; but thyroid feeding of such animals raises the nitrogen output and restores the sparing power of fat and carbohydrate. In normal fasting dogs after severe labor adrenalin still produces glycosuria and increases protein destruction; fat-feeding increases this glycosuric effect. In thyroidectomized dogs, adrenalin produces no glycosuria even on carbohydrate diet; but after thyroid feeding, adrenalin glycosuria occurs in such animals. Phloridzin causes the same glycosuria in thyroidectomized as in normal animals. In depancreatized dogs, adrenalin greatly increases the excretion of both sugar and nitrogen; D/N may exceed 7. Preliminary

removal of the thyroid almost entirely prevents the increased protein destruction usually following pancreatectomy. Prolonged treatment of either normal or thyroidectomized animals with thyroid extract gives rise to the adrenalin-mydriasis phenomenon of Loewi. The Bernard puncture produces no glycosuria in thyroidectomized dogs. Pilocarpin stimulates the autonomic (vagus) nerve governing the pancreas; therefore given with adrenalin it prevents glycosuria. Atropin inhibits the pancreas; therefore it renders adrenalin glycosuria possible even in thyroidectomized animals. The second paper of Eppinger, Falta and Rudinger is devoted especially to the parathyroids. In thyreoparathyroidectomized animals, the dextrose tolerance is markedly lowered, and adrenalin produces intense glycosuria. Extirpation of three parathyroids temporarily diminishes the dextrose tolerance. Removal of the pancreas and three parathyroids results in high nitrogen-excretion and a higher D/N ratio than simple pancreatectomy. After removal of both adrenals, phloridzin produces little or no glycosuria. In both papers, the authors refer to clinical conditions, especially the tendency to glycosuria in hyperthyroidism and the increased sugar-tolerance in myxœdema and Addison's disease. They conclude essentially that the thyroid and chromaffin system stand opposed to the pancreas and the parathyroids. A disturbance of balance may result from either over-function of one set or under-function of the other.

The views of these authors have been widely accepted in texts and current literature. Biedl (3) gives them much prominence. Von Noorden [(1), p. 170 ff] adopts them and gives a corresponding diagram. Minkowski has stood firmly against these teachings. Opie [(4), p. 117] refers to them as "ingenious speculations." The evidence on the subject may be reviewed under the following headings:

1. The thyroid in relation to glycosuria and diabetes.
2. The parathyroids in relation to glycosuria and diabetes.
3. The adrenals in relation to glycosuria and diabetes.
4. The hypophysis in relation to glycosuria and diabetes.
5. Antagonisms between portions of the nervous system.
6. Antagonisms between drugs.
7. Other glandular inter-actions.

1. The Thyroid in Relation to Glycosuria and Diabetes.

This topic may be considered in the following subdivisions:

A. Glycosuria associated with hyperthyroidism.

B. Increased sugar-tolerance associated with thyroid deficiency.

C. Relations between the thyroid and diabetes.

D. Interpretation of the evidence.

A. Glycosuria Associated with Hyperthyroidism.

(I) *Clinical.* — The tendency to spontaneous glycosuria or easy alimentary glycosuria in Basedow's disease is well known. Chvostek gave high figures for this complication, and Kocher found it frequent. The subject is discussed by Magnus-Levy (4*A*), Glaessner (2), and Garrod (3). For a referat of the general subject of the thyroid, see Bircher. On the whole, spontaneous glycosuria occurs in only a relatively small number of cases. Aschner (1) has described an excessive sensitiveness of Basedowoid patients to adrenalin, but it is noteworthy that this sensitiveness does not take the form of glycosuria.

Human patients have developed glycosuria from the use of thyroid preparations. Ewald [ref. by Garrod (3)] reported glycosuria as high as 6 per cent from the use of thyroid extract, in a woman with myxœdema. Notthaft [ref. by Garrod (3)] described the case of a man who, in order to reduce his weight, took about a thousand 5-grain tablets of thyroid extract within 5 weeks. He developed symptoms of Graves' disease, with a polyuria of three litres per day, and about 1 per cent sugar in the urine. Glycosuria disappeared without restriction of diet within ten days after stopping the use of thyroid extract.

(II) *Experimental.* — According to Biedl [(3), p. 89] the symptoms of clinical hyperthyroidism may be imitated more or less perfectly in laboratory animals by excessive doses of thyroid. The results however are variable, not constant. In addition to eye-symptoms, various organ-changes, increased nitrogen excretion, etc., authors have sometimes observed emaciation, polyphagia, polydipsia, polyuria and glycosuria. Carlson, Rooks and McKie have shown that though toxic symptoms may thus be produced in animals, the effects are not strictly comparable to those of hyperthyroidism in man. That the toxicity is specific

to the thyroid was proved by French, who fed a series of animals with various other organs in comparison with thyroid. Glycosuria from thyroid feeding in animals is not necessarily specific, for Rosenberger (p. 106) notes that large quantities of pancreatin fed to rabbits may produce glycosuria.

B. Increased Sugar-tolerance Associated with Thyroid Deficiency.

(I) *Clinical.* — Increased dextrose-tolerance is the rule in clinical hypothyroidism, but important exceptions (to be mentioned later) must also be reckoned with. Hirschl [ref. by Magnus-Levy (*4A*)] failed to reach the limit of tolerance in two myxœdema patients by feeding respectively 200 g. and 400 g. dextrose. Knöpflmacher [ref. by Magnus-Levy (*4A*)] made similar observations upon cases of sporadic cretinism. Authors are agreed that thyroid treatment tends to bring the limit of assimilation down to normal. Siegmund has reported that thyroid deficiency in children is often accompanied by a pathological sugar-hunger. Such children are able to take large quantities of sugar for long periods without glycosuria, and the sugar appears to act beneficially upon the effects of the thyroid deficiency. Thyroid feeding may cure this sugar-hunger within two days.

(II) *Experimental.* — As Eppinger, Falta and Rudinger first proved, removal of the thyroid with preservation of the parathyroids renders alimentary glycosuria difficult. Their assertion that adrenalin fails to produce glycosuria in thyroidectomized animals has been modified by later authors [see Chapter XVI]. McCurdy, working with the Blumenthal intravenous method, found that thyroidectomy raises the assimilation limit for dextrose; and if the parathyroids are preserved, this result is permanent.

C. Relations Between the Thyroid and Diabetes.

(I) *Clinical.* — The simultaneous occurrence of hyperthyroidism with diabetes has attracted attention, and has been put forward as evidence for the polyglandular hypothesis. But authors [von Noorden (1), p. 214; Magnus-Levy (*4A*); Garrod (3)] now properly emphasize the fact that the combination is rare; and that the time-relations of their onset indicate not the production of one disease by the other, but rather the origin of

both from either common or independent causes. Diabetes and exophthalmic goitre have been found in different members of the same family. Blachstein [ref. by von Noorden (1), p. 216] has claimed a frequent enlargement of the thyroid in diabetes, but is contradicted by von Noorden's extensive experience. In a few instances, diabetes has developed following treatment with thyroid extract, but the cases are supposed to have been latent preëxisting diabetes. Grawitz [ref. by Magnus-Levy (4*A*)] observed increase of diabetic glycosuria from thyroid treatment. Garrod (3) refers to a few cases in which exophthalmic goitre was associated with atrophy or other lesions of the pancreas.

Due attention must also be paid to the existence of glycosuria or diabetes in conjunction with thyroid deficiency. Cases of this sort are referred to by Garrod (3), by Lepine [(1), p. 330], and by Magnus-Levy [(4*A*), p. 1004], and by Opie [(4), p. 357].

Schmidt and Salomon, Falta (7), and Garrod [(3), a doubtful case] have reported instances of fatty stools in connection with hyperthyroidism. The significance of the condition is rightly questioned by Garrod.

(II) *Experimental.* — The supposed antagonism between thyroid and pancreas, as observed by Eppinger, Falta and Rudinger, has been described; it applies to both the sugar and nitrogen excretion. Bircher (p. 109 ff) lays emphasis upon their views. The "slowing of metabolism" in thyroid deficiency is well known. Marinesco and Parhon proved that thyroidectomized animals can survive longer starvation than normal animals. Even as early as 1904, Lorand had advanced the idea that the pancreas and thyroid stand in opposition. He claimed that if the thyroid is removed (sparing the parathyroids) two days after pancreatectomy, the glycosuria disappears; also that removal of the pancreas is followed by signs of over-function of the thyroid, and removal of the thyroid is followed by hypertrophy of the islands of Langerhans of the pancreas. Such islet-changes were also alleged by Falta and Bertelli [see Falta 4*A*]. Tiberti [ref. by Lepine (1), p. 366] found, in two dogs which died 7 hours after pancreatectomy, changes like those described by Lorand, viz., enlargement of the thyroid, and swelling of all its follicles with colloid. Licini likewise, from histologic studies at different periods after pancreatectomy, concluded that a marked increase of thyroid function occurs, and that the changes become more marked the longer the diabetes has existed.

MacCallum (2) twice performed thyroidectomy following pancreatectomy. The result in one animal (pancreatectomy not quite complete) was cessation of glycosuria; in the second animal the glycosuria diminished somewhat.

D. Interpretation of the Evidence.

The interpretation suggested by Eppinger, Falta and Rudinger has been mentioned. Falta (7) reviews the literature of glycosuria associated with clinical hyperthyroidism, and concludes that the thyroid secretion opposes the pancreas, by an action either upon the gland or upon the secretion which it forms. On the contrary, Glaessner (2) classifies thyroid glycosuria with other non-diabetic forms. The evidence may be reviewed as follows.

(I) *Clinical.* — The glycosuria accompanying Graves' disease may very easily be explained on a toxic or nervous basis. Thyroid extract produces merely a toxic glycosuria. Adrenalin is a more powerful glycosuric agent than thyroidin, and since we have seen [Chapter XVI] that adrenalin glycosuria is unconnected with the pancreas or diabetes, we have reason to suspect that the same may be found true of thyroid glycosuria. With regard to the increased sugar-tolerance in thyroid deficiency, Magnus-Levy (44) properly suggests that it may be largely due to the known slowness of absorption. Since the function of all organs is sluggish, the kidney may be less permeable for sugar; thus the findings with the Blumenthal test may be explained. It is possible that the tissues do possess an increased power of using sugar, but the fact has never been demonstrated. Information might be derivable from the subcutaneous method; or an objection-free way would seem to be by slow continuous intravenous infusion of dextrose, with repeated blood-sugar tests. The association of diabetes with exophthalmic goitre indicates rather plainly that no specific effect of the thyroid over-function is involved, because the association is so uncommon. A specific thyroid influence in diabetes is rendered further improbable by the practical absence of thyroid changes in diabetics. Finally there is the important fact that glycosuria and diabetes may also be associated with thyroid *deficiency*. It thus becomes probable that coëxisting diabetes and thyroid disorders are both manifestations of some underlying cause or causes. For analogy, we may refer to the cases of simultaneous disorder of several glands, as reported by

Apert, and by Claude and Gougerot. Falta (9 and 10) has recently described similar cases. Cohn and Peiser have described symptoms of hyperthyroidism in patients with organic pancreatic disease, without diabetes. Faure-Beaulieu, Villaret and Sourdel have reported concerning a case of simultaneous atrophic and inflammatory changes in the pancreas, thyroid and adrenals. The statement will hardly be questioned, that a patient with disorder of one gland is more prone than a normal person to disorders in other glands; the nervous or other fundamental tendency is there. The association of diabetes and Bright's disease is explained thus, and not by any "Wechselwirkung" of pancreas and kidney; and the association of diabetes and hyperthyroidism likewise receives its most natural explanation on this basis. Only thus is it possible to understand cases such as mentioned by Lepine [(1), p. 445] in which diabetes begins some time after the cure of Basedow's disease. This view is also accepted by Opie [(4), p. 357], who cites similar cases. In view of the rarity of the combination of diabetes with thyroid changes, it cannot be said that clinical evidence points to a specific influence of the internal secretion of the thyroid in diabetes.

(II) *Experimental.* — Lorand's assertion concerning hypertrophy of the islands of Langerhans after thyroidectomy still awaits confirmation. The variations of these structures are too numerous and too little understood to justify conclusions which seem to rest upon examination of a few sections from the pancreas of one thyroidectomized dog. The observations of thyroid overfunction after pancreatectomy are interesting but entirely uncontrolled. We lack information as to how the thyroid behaves after ablation of other abdominal viscera, or as to the findings after partial extirpation of the pancreas. A state of systemic intoxication, such as follows pancreatectomy, might well give rise to a non-specific hyper-function of the thyroid. The effect of the nervous disturbance is another possible explanation. A specific relation between the thyroid state and diabetes is rendered improbable by the normal thyroids of most human diabetics, and by my long series of dogs with intense diabetes and normal thyroids. Attention should also be given to the finding by Pratt (2), that in dogs in which extreme pancreatic reduction (atrophy, without diabetes) had existed for 5 to 34 months, the thyroids were found scarcely recognizable on account of disappearance of colloid and atrophic (instead of hypertrophic!)

changes. Accordingly, it may be that through the nervous system or otherwise, pancreatic disturbance may be followed by thyroid changes; but the assumption of a specific antagonism, or of over-function of one gland in causal connection with under-function of the other, is not supported by the facts.

Concerning the influence of thyroidectomy upon diabetes, Lorand himself acknowledged that the duration of life was shortened. Cachexia, weakness, or nervous shock may therefore account for the failure of glycosuria, somewhat as after cutting the spinal cord. In MacCallum's incompletely depancreatized dog, glycosuria ceased after thyroidectomy and the animal died in three days. In his completely depancreatized dog, glycosuria diminished after thyroidectomy and the animal died the next day. Without other criticism of Eppinger, Falta and Rudinger's results, we may accept the fact that after removal of the pancreas a dog has diabetes, and after removal of the thyroid he has myxœdema, and after removal of both organs he has both conditions. There is no special significance in this. The myxœdematous animal indeed excretes less sugar, because his sluggish organs with their impaired functions can produce it less readily. But many different causes may diminish diabetic glycosuria. Glycosuria is not a measure of diabetes. Eppinger, Falta and Rudinger failed to prove that thyroidectomy gives the diabetic animal any power to *utilize* sugar. As a matter of fact, the depancreatized animal is just as diabetic, just as completely unable to utilize dextrose, after thyroidectomy as before. He has merely suffered another metabolic injury in addition to his diabetes. The case is similar as respects nitrogen. Obviously, myxœdema will make metabolism more sluggish in either a non-diabetic or a diabetic animal. The fact is without special significance, and without benefit to the animal, which dies more quickly than from simple diabetes. The chief fallacy of the whole matter lies in attempting to relate the increased nitrogen-loss of hyperthyroidism with the increased nitrogen-loss of diabetes. Obviously, all we get in the urine is the end-result; the elevation of total nitrogen gives no information concerning the process which brought it about. That similar effects necessarily result from the same cause is a fallacy in logic and in physiology. The causes that increase total nitrogen are sufficiently numerous, that no basis is afforded for concluding that the processes leading to this result in hyperthyroidism and in diabetes are the same. It seems probable that

the nitrogen-increase of hyperthyroidism is more closely related to that of fever than it is to that of diabetes; for both the former are of some sort of toxic or nervous origin, while the latter is due to the absence of the internal secretion of the pancreas.

2. The Parathyroids in Relation to Glycosuria and Diabetes.

Mention has already been made of the findings of Eppinger, Falta and Rudinger, that parathyroidectomy lowers sugar-tolerance, and that removal of three parathyroids in depancreatized animals increases the glycosuria and the D/N ratio. The earlier results with panthyroidectomy belong in this category, for the effects were essentially those of parathyroid, not of thyroid loss. Falkenberg [ref. by Lepine (1)] observed glycosuria in 13 of 20 thyroidectomized dogs; in one, it persisted 3 weeks; in two others, 8 days; and in the others it was irregularly intermittent. Gley found slight, transitory glycosuria in 4 out of 6 thyroidectomized dogs, but missed it in rabbits [because, owing to their different location, the external parathyroids escaped removal in these animals]. Hirsch (2 and 3) found that panthyroidectomy produces a lowering of dextrose-tolerance in dogs; but it appears not immediately, but only along with the other symptoms of tetany, hence may be attributed to the disorder of the nervous system. Underhill and Saiki injected dextrose subcutaneously in totally thyroidectomized dogs. In the longer of their two experiments, a dog in tetany received a dose of 25 g. dextrose on November 6; it died on November 12, with glycosuria still persisting, and in the meantime had excreted nearly half the injected dose. From studies of the liver-glycogen, the authors conclude that panthyroidectomy injures not the glycogenic but the oxidative power of the body.

We must conclude from the experiments of Eppinger, Falta and Rudinger that the influence of the parathyroids is not upon the pancreas nor upon its secretion, since the usual effect of parathyroidectomy is observable in depancreatized animals. Removal of the parathyroids is followed by tetany, not diabetes; the tetany may sometimes be accompanied by slight glycosuria; but there is no clinical or experimental evidence that the parathyroids stand in any causal relation with diabetes. Underhill's dog was not glycosuric before the dextrose injection; the impression is given that the injection was responsible for the ensuing

glycosuria which lasted six days; not only is Underhill's conclusion of diminished oxidative power justified, but the possibility of a preternaturally slow absorption of the injected sugar seems indicated. A similar abnormality is represented in the observation of Hirsch (2), that some of these dogs after amylodextrin feeding may excrete the same dextrin unchanged in the urine. As pointed out in a former chapter, this involves a double anomaly, for higher dextrins are normally not absorbed as such, and if injected are broken down by the kidney. From such facts we obtain an idea of the metabolic prostration accompanying tetany, and it is seen that a failure properly to utilize sugar is not surprising. Underhill's tables show that oliguria rather than polyuria accompanies the glycosuria. The evidence that the glycogenic power is retained assists toward the general conclusion that the condition is entirely distinct from diabetes. The absence of parathyroid lesions or tetanoid symptoms in human diabetics strengthens this opinion.

Attempts are still being made to explain tetany and locate the point of attack of the hypothetical poison [see papers of Carlson and Jacobson, together and separately]. MacCallum (3) has lately reviewed the subject, and has shown the effect of tetany-blood upon the peripheral nerves; if by cross-transfusion, the limb of an animal in tetany is supplied with blood from a normal animal, the nervous condition in the limb becomes normal; and the hyperexcitability returns when the tetany-blood is allowed to circulate in the limb again. From this and other experiments, he concludes "that spasms of the muscles come only when the ganglion cells send out abnormally violent impulses to abnormally sensitive nerve-endings." Since the muscular disturbances are of both central and peripheral nervous origin, it becomes probable that the glycosuria may be similarly produced. The lowering of sugar-tolerance and the increased intensity of adrenalin or diabetic glycosuria when three parathyroids are removed may best be interpreted as a mild or latent tetany; the nervous condition is present, but not to the degree of spasms. Nervous hyperexcitability is the principal feature of parathyroid tetany, and readily explains the occasional slight glycosuria. There is no evidence that the parathyroids take any specific part in carbohydrate metabolism.

3. The Adrenals in Relation to Glycosuria and Diabetes.

The subject may be considered under the following divisions:

A. Deficiency of adrenalin.

B. Excess of adrenalin.

C. Antagonism between pancreas and adrenals.

A. Deficiency of Adrenalin.

Eppinger, Falta and Rudinger, Porges (1 and 2) and other authors have brought into relation hypoglycemia, weakness and deficiency of adrenalin in Addison's disease. Schirokauer (2) found that hypoglycemia may occasionally be absent in this disease; but its presence in most cases is established by the work of Bernstein. Neubauer and Porges consider that the loss of glycogen, weakness, and hypoglycemia of phosphorus poisoning are due to disabling of the chromaffin system. Porges recommended carbohydrate diet for Addison patients, and Pitres and Gautrelet [see Gautrelet (4)] claimed benefit in one case. But clinically, both carbohydrate and adrenalin in the treatment of Addison's disease are failures; and experimental evidence is reviewed by Bayer [(2), p. 98] showing that hypoglycemia, weakness and deficiency of adrenalin do not necessarily go together. In Chapter XVI was mentioned the proof that the symptoms (hypoglycemia, weakness, loss of liver-glycogen) following double epinephrectomy are not due to lack of adrenalin. With respect to diabetes, Mayer (2) tried the effects of simultaneous pancreatectomy and epinephrectomy, but the animals died too quickly to permit conclusions. Frouin (2) removed one adrenal and two-thirds of the other, then the pancreas a month later. One of the two dogs lived 25 hours, the other 6 days. The author considered that the diabetes was less severe, but the conclusion cannot be accepted, at least in any specific sense, for partial epinephrectomy cannot be expected to produce such a result. Zuelzer (2 and 3) found that ligation of both adrenal veins simultaneously with pancreatectomy prevents or diminishes glycosuria; but the longest survival was 36 hours, and the extreme prostration is a sufficient explanation. The increased sugar-tolerance which some have claimed in Addison's disease is not very marked, and may readily be explained by defective absorption or other non-specific causes; there has never been the slightest evidence to demonstrate an

over-function of the pancreas in such conditions. On the other hand, Garrod (3) mentions a case reported by West, with a combination of complete atrophy of the adrenals, pigmentation of the skin, and severe diabetes. Also Montgomery has recently described a case of tuberculosis of both adrenals, with diabetes; in the same patient there was a question of thyroid atrophy. It is thus sufficiently clear that even extreme adrenal insufficiency does not prevent diabetes; and the diabetes, as in West's case, may be very severe.

B. Excess of Adrenalin.

Logically, according to the polyglandular doctrine, there should be an excess of adrenalin in diabetes. The statements and diagrams of the upholders of this doctrine plainly indicate a connection between under-function of the pancreas and over-function of the chromaffin system, and vice-versa. But Bröking and Trendelenburg proved that there is no relation between diabetic glycosuria and the adrenalin content of the blood. Bittorf likewise showed the absence of adrenalin increase in diabetic blood; one of his cases combined intense hyperglycemia with extreme atrophy of the pancreas, yet adrenalinemia was not present. Ingier and Schmorl found that the adrenalin content of the adrenals of diabetic patients at autopsy is actually diminished. Loewit (3) found that adrenalinemia is absent in the pancreas-diabetes of frogs. Futcher [(1), p. 758] justly sums up the facts in the sentence, "There is no clinical or pathological evidence showing that diabetes bears any intimate relationship to disease of the adrenal glands."

C. Antagonism Between Pancreas and Adrenals.

As mentioned in Chapter XVI, adrenalin does not produce its glycosuric effect by any action upon the pancreas nor upon its internal secretion. Tiberti (3) proved that long-continued dosage with adrenalin produces no anatomical change in the pancreas or its islets. Langley stated that adrenalin does not start a flow of pancreatic juice, but increases a flow already in progress. Benedicenti, also Glaessner and Pick (2), showed that large doses of adrenalin inhibit pancreatic secretion. Bickel found that a series of drugs, of which adrenalin is one, inhibit the pancreatic flow. Sweet and Pemberton found such an inhibition after

intravenous injection of either adrenal or hypophyseal extract, and attributed a specific importance to the phenomenon. Later they added the observation that removal of both adrenals gives rise to a flow of pancreatic juice. For comparison, mention should be made of the work of Nürenberg, who, using dogs with pancreatic and intestinal fistulæ, showed that the administration of iodothyreoglobulin stimulates pancreatic secretion. The contrast between the action of the two supposed "antagonists" of the pancreas is here evident. Edmunds effectually disposed of the idea of a specific relation of adrenalin and pancreas, by showing that a variety of agencies which raise blood-pressure and produce anemia of the pancreas (strophanthin, barium chloride, asphyxia, splanchnic stimulation, and especially nicotin) serve also to inhibit pancreatic secretion. Gley [see Gley (2) and Popielski (3)] came to a similar conclusion. The increased flow following epinephrectomy may probably be brought into relation with the findings of Popielski (1) that lowering of blood-pressure increases pancreatic secretion. The suggestion of such a non-specific action has been confirmed by the latest publication of Pemberton and Sweet, showing that pancreatic secretion occurs when low blood-pressure follows epinephrectomy; it stops when adrenalin injection raises the blood-pressure, and begins again when the pressure falls. The notion of a specific antagonism is not only experimentally refuted, but loses significance still further from the fact that the alleged antagonism concerns not the internal but the external function of the pancreas. Attempts to influence the internal function of the pancreas through the vagus [see below] or through secretin [see Chapter XVIII], or through any other agencies known to stimulate the external function, have all proved failures. In Chapter XXII, I shall present experiments which indicate that, if there is any relation at all between the internal and external functions of the pancreas, it is one of opposition.

On the other hand, influences of the pancreas upon the adrenals have been claimed. Glaessner and Pick (2) found that the adrenals of animals with pancreatic fistula show almost complete absence of chromaffin substance, and changes in the medullary cells; and the extract of these adrenals has no blood-pressure-raising effect. Bruckner and Jianu established pancreatic fistulæ in 20 dogs, and found rapid emaciation and death, on an average within 7 days after operation; and the adrenal fat was found to

have disappeared. The simple emaciation was shown not to be the cause, inasmuch as a dog starved for 11 days still showed abundant lipoid-granules in the adrenal cortex. In consequence of experiments by Minami, and criticisms by Wohlgemuth (7 and 8), it is now agreed by all, including Glaessner and Pick (4), that the changes in question occur only in a minority of fistula-dogs, from unknown causes; they can therefore not be interpreted as specific. And since injury of one organ leads to injury of the other, they obviously do not speak for an antagonism.

Diminution of eosinophile cells in the blood was also used by Falta and co-workers as evidence for the similarity between pancreatic deficiency and adrenal excess; it was found by them both after pancreatectomy and after adrenalin injection. But Weichselbaum and Lubarsch [ref. by Gigon (2)] found otherwise; the latter in particular observed eosinophile cells in the pancreas itself in clinical cases of severe "pancreatic" diabetes. Also, Caro has recently published blood-counts of 28 diabetics; in 8 there was distinct eosinophilia.

Especially Zuelzer (2, 3, 4) has identified adrenalin glycosuria with diabetes. This author (2) discovered that adrenalin glycosuria is inhibited by a preliminary injection of pancreatic extract. Zuelzer, Dohrn and Marxer prepared a supposed "hormone" from the pancreas subjected to stasis, undertook to standardize the preparation by its efficiency in preventing adrenalin glycosuria in rabbits, and proposed it as a therapeutic agent in diabetes. Makaroff confirmed the inhibition of adrenalin glycosuria by pancreas-extract. Ghedini claimed to inhibit both the pressor effect and the fatal result of large adrenalin injections by extracts of pancreas. Biedl and Offer repeated such experiments, with uncertain and contradictory results. But they found that thoracic-duct lymph, even when freed from albumin by alcohol, could inhibit the glycosuric action of adrenalin, and also the mydriasis of the frog's eye But hirudin or extract of crab's muscle had the same effect as lymph. The hemodynamic effects of adrenalin were not neutralized by lymph. Glaessner and Pick (2) found that injection of pancreatic juice simultaneously with, though in a different area from, an adrenalin injection prevents glycosuria. The pancreatic juice does not prevent adrenalin mydriasis; the juice itself contains mydriatic substances. Witte-peptone was found to act like pancreas preparations in inhibiting adrenalin glycosuria. Frugoni (2) confirmed the prevention of adrenalin

glycosuria by pancreatic extract and juice. He also found that if an animal be kept saturated with sodium carbonate by means of large subcutaneous injections, adrenalin fails to produce either toxic or glycosuric effects, presumably because it is chemically modified. But alkalinity and salts are not the only factors, for neutralized pancreatic juice destroys adrenalin in vitro, and dialyzed pancreatic juice has no effect upon adrenalin. Comessatti (2), on the contrary, could find no destruction of adrenalin by pancreas or other organ extracts *in vitro*, and concludes that there is no chemical antagonism between the substances. Wolownik [ref. by Lepine (1), p. 302] found that spermin injection delays adrenalin glycosuria. Gautrelet (1, 2, 3) attributed the adrenalin-neutralizing effects of pancreas and other organ-extracts to their cholin content, but Frank and Isaac (2) came to contrary results. Schrank discovered that calcium chloride acts as an antagonist to adrenalin as regards dilatation of the frog's pupil and glycosuria in rabbits. In connection with the reported prevention of glycosuria by pancreas extract, should be remembered the demonstration by Leschke (1), Pariset (1 and 2), and others, that pancreas extract itself may cause glycosuria. Tomaczewski and Wilenko proved that all lymphagogues can suppress adrenalin glycosuria. Fever (Aronsohn) or renal injury (Ellinger and Selig) may likewise prevent adrenalin glycosuria. Forschbach (2) experimented with Zuelzer's "hormone" in depancreatized dogs and human diabetics; he found a slight temporary diminution of glycosuria, which he attributed to fever and systemic and renal injury. According to Gautrelet and Thomas, even normal serum may neutralize the glycosuric action of adrenalin. The work of Fürth and Schwarz is especially important; they proved that even the intraperitoneal injection of such substances as turpentine or aleuronat may prevent adrenalin glycosuria. The effect of pancreas extract and all the whole long list of similar "inhibitory" substances is merely toxic. Only the permeability of the kidney is affected, and blood-analyses show that the usual adrenalin hyperglycemia occurs just the same. In accord with this evidence is the fact that adrenalin glycosuria is inhibited by drugs which damage the kidney, notably glutaric and tartaric acids. Miculicich found that hirudin and ergotoxin diminish both the renal permeability and the hyperglycemia in adrenalin glycosuria.

The effect of various agencies upon adrenalin glycosuria is readily explained, as an increase when they themselves tend to

glycosuria, or when they augment the nervous stimulation produced by adrenalin, or increase the permeability of the kidney; and as a decrease when they oppose the nervous stimulation by adrenalin, or by toxicity damage either the sugar-forming or sugar-excreting function. There is no evidence of any kind indicating a specific antagonism between the adrenals and the pancreas.

4. The Hypophysis in Relation to Glycosuria and Diabetes.

In polyglandular writings the hypophysis is currently classified along with the thyroid and adrenals as an "antagonist" of the pancreas. Aschner (2) has arrived at the same conclusions. The state of the experimental evidence was noticed in Chapter XII. Clinically, a large proportion of acromegalics have an abnormally high sugar-tolerance; another large percentage have diabetes; and the same patient may pass from one extreme to the other. Claude and Baudouin have described the organs of an acromegalic woman, whose disease began in 1885, and who died in 1911. The case was typical acromegaly. Menstruation stopped in 1885, when the patient was 25. Hypertension was a prominent symptom. Autopsy showed an adenoma of the hypophysis weighing 48 g. The uterus was small, the ovaries atrophic. The adrenals, greatly enlarged, together weighed 17.5 g. The thyroid, greatly hypertrophied, weighed 190 g. Four hypertrophied parathyroids were also dissected out. Microscopically, evidences of over-function of adrenals, thyroid and parathyroids were plain. Nothing is stated concerning the pancreas. The important feature is that in this patient with demonstrable hypertension and marked over-function of both thyroid and adrenals, with enormous en-enlargement of the hypophysis, there was no sign of diabetes at any time.

Since there is no constant relation between hypophyseal disease and either diabetes or the opposite extreme of exaggerated sugar-tolerance, and since acromegalic diabetes is frequently accounted for by demonstrable pancreatic changes, it is evident that the attempt to classify the hypophysis as a specific "antagonist" of the pancreas is arbitrary and unsupported.

5. Antagonisms between Portions of the Nervous System.

Back of the secreting glands themselves, there has been assumed a balance or antagonism between the portions of the

nervous system governing them. Different types of diabetes have been explained on the basis of a supposed inhibition of the pancreas as the principal element in some cases, and stimulation of antagonistic glands as the principal element in other cases. The view may be summed up in the following quotation from Falta (6). "Es lässt sich . . . jede diabetische Stoffwechselstörung definieren als ein Ueberwiegen sympathischer Impulse über die autonomen. Liegt die Ursache hiefür mehr in einer Insuffizienz des Pankreas, so können wir von einem pankreatogenen, liegt sie mehr in einer Ueberfunktion des zirkulären Systems, so können wir von einem adrenalinogenen Diabetes sprechen." Halasz (2) has accepted the view that some cases of diabetes are perhaps not of pancreatic origin; and there are many similar expressions in the literature. An interesting observation is that of Loewi (3) concerning adrenalin mydriasis; viz., that in normal dogs, cats and human beings, adrenalin instillation is without effect upon the pupil, but in depancreatized animals it causes mydriasis; the reaction is present in many human cases of hyperthyroidism, and a slight reaction is claimed in a few cases of human diabetes. The phenomenon may well be accepted as evidence of an abnormal nervous state, and if positive in human diabetes, would agree well with the suggestions in previous chapters concerning diabetes as a disease of the nervous system. But unfortunately, the outcome is negative in the great majority of cases of human diabetes; when positive, it is perhaps due to one of the frequent associated nervous states; and it gives no specific information concerning the nature of human diabetes.

The chief objection to the sympathetic-autonomic speculation concerning diabetes is that the internal secretion of the pancreas is probably not under the control of the vagus [Chapter XVII].

6. Antagonisms between Drugs.

In Chapter XVI were mentioned the actions of various drugs upon the sympathetic and autonomic nervous systems. These substances have been used in many experiments in connection with the polyglandular doctrine. The supposed antagonistic effects of cholin and adrenalin have previously been mentioned [Gautrelet, Pal, Frank and Isaac, and others]. Nothing of significance for diabetes has come from the study. Over-function of the chromaffin system through sympathetic stimulation is

assumed to cause increased sugar-formation in diabetes; nicotin paralyzes sympathetic ganglia; yet nicotin is without effect upon the glycosuria of diabetic dogs (Masudo). The claims of Eppinger, Falta and Rudinger concerning the effects of atropin and pilocarpin were mentioned at the opening of this chapter. Falta, Newburgh and Nobel state that when adrenalin glycosuria does not occur, it can generally be produced by preliminary treatment with atropin; when it is present, it can generally be inhibited by injection of pilocarpin. The fact remains that pilocarpin is useless in diabetes. Also, atropin has recently been strongly recommended by Rudisch, commended by Forchheimer, and found ineffective by Mosenthal; it at any rate fails to aggravate diabetes. One thing is certain; the polyglandular doctrine has never proved of any use when put to any concrete practical test.

7. Other Glandular Interactions.

As stated at the outset of this chapter, the thyroid has been regarded as the ally of the adrenals by Eppinger, Falta and Rudinger and their followers. Asher and Flack have claimed that the thyroid secretion increases the excitability of the depressor nerve, and the effect of adrenalin upon the blood-pressure. They regard the coöperative action of the thyroid and the adrenals as the cause of symptoms in certain diseases. Caro reported that after injection of thyroid juice, the serum of rabbits and dogs acquires the mydriatic action on the frog's eye, and also the ferric chloride reaction, characteristic of adrenalin. His paper contains an extreme statement of the polyglandular ideas. Fraenkel reported increased adrenalin content of the blood in patients with hyperthyroidism. But Bröking and Trendelenburg found no increase of adrenalin in the blood of such patients, and Ingier and Schmorl found no increase of adrenalin in the adrenals at autopsy. The studies of G. N. Stewart are sufficiently convincing and conclusive concerning the absence of adrenalinemia, in hyperthyroidism and other conditions, and the unreliability of the methods on which the positive claims have been based.

The adrenals have also been drawn into relation with renal disease, as with practically all other recondite disorders. Von Noorden [(1), pp. 110–11] accepts adrenalin as the cause of the high tension and high blood-sugar of nephritis, on the usual polyglandular basis. The subject is reviewed in admirable fashion

by Bayer [(2), p. 56 ff]. The matter was first called to attention by French writers, who reported cortical adenomata of the adrenals in connection with nephritis and related conditions, till Wiesel proved that such formations can be found in nearly all adrenals. Schur and Wiesel then claimed positive chemical and biological proof of increased adrenalin in nephritic blood, and also positive results from animal experiments with renal injuries. A host of experimental and clinical studies of the anatomical changes and adrenalin content of the adrenals, and the adrenalin content of the blood, were then undertaken [for references, see Bayer]. Goldzieher and Molnàr found adrenal changes apparently confirming Schur and Wiesel's views, but Aubertin and Clunet, Cohn [see Aschoff], Bittorf [see Bayer (2)], and Goldschmidt proved the entire absence of relationship between adrenal changes and either hypertension or cardiac hypertrophy. Numerous studies of the adrenalin content of nephritic adrenals have led to variable results and have failed to show any constant increase. Pribram discusses the conflicting literature concerning the adrenalin content of nephritic blood. Any constant increase is fully ruled out by the investigations of Bittorf, Wirz, Fraenkel, Stewart, and Janeway and Park. One of Bittorf's cases presented a combination of diabetes, nephritis, hypertension and apoplexy; there was no increase of adrenalin. Furthermore, reactions supposed to indicate increase of adrenalin have been found in cases without nephritis and without increased pressure. The excretion in the urine of substances giving adrenalin-like reactions has been proved to be without significance. The self-contradictions of the polyglandular doctrine are apparent here as elsewhere; for if over-function of the adrenals produces hypertension in nephritis, why does not the alleged over-function in diabetes produce hypertension? Concerning blood-sugar the evidence is equally clear. Neubauer reported hyperglycemia in nearly all nephritic patients examined, and attributed it along with the hypertension to adrenal over-function. Weiland (2) found no hyperglycemia in nephritis except in connection with uremia, eclampsia or apoplexy. Frank found hyperglycemia absent in 10 cases of increased pressure, with or without nephritis. Stilling failed to confirm Neubauer's findings. Tachau (1) found no abnormal blood-sugar values in cases of nephritis without uremia, even when 100 g. dextrose was fed. Hegler found elevation of blood-sugar in nephritis, but normal values in cases of hypertension without nephritis. It is

therefore clear that hyperglycemia is not a constant accompaniment of either nephritis or hypertension.

In Chapter XII were mentioned the polyglandular explanations of the occasional glycosuria of pregnancy, and it was pointed out that this glycosuria is not known to be due to excessive function of the adrenals or any other gland, and especially (except in true diabetic patients) does not arise from any absolute or relative insufficiency of the pancreas. Schur and Wiesel claimed to find adrenalinemia in muscular labor, the increase being supposedly for the purpose of mobilizing more sugar for the working muscles; but Bayer [(2), pp. 97–98] has shown that the opinion is untenable. Mention has been made in previous chapters of the supposed importance of the adrenals in diabetes insipidus, osteomalacia, rickets, starvation, etc., and the small probability of such ideas.

Bayer [(2), p. 123] refers to Feodosjeffs, who found. hypertrophy of the adrenals after removal of the ovaries; also to Parhon and Golstein, who found, in bitches killed 24 days to $2\frac{1}{2}$ years after oöphorectomy, no changes in the adrenals except a doubtful increase of the cortical lipoid. Schenk has recently shown that castration is followed by hypertrophy of the adrenals, limited to the cortex, and associated not with an increase but with a decrease of adrenalin. Similarly, the thymus has been brought into relation with the adrenals. Enlargement and congestion of the thymus have been found to follow epinephrectomy; Addison's disease is sometimes associated with persistent thymus or status lymphaticus; under certain conditions injection of adrenalin may produce hemorrhages in the thymus, etc. [see Bayer (2), p. 100]. Observations of this sort are of interest, as showing the effects of injury or removal of one organ upon other organs. They obviously offer no support for those fantastic notions of antagonism which constitute the polyglandular doctrine.

Experiments.

In previous chapters it was found that certain prevailing ideas concerning the pancreas are incorrect, and that a severe form of diabetes may be obtained when a considerable mass of pancreatic tissue still remains in its normal location. Furthermore, contrary to existing ideas, the removal of any large proportion of the pancreas (*e.g.*, three-fourths) is not a matter of indifference to the organism, but is followed by a permanent and

plainly demonstrable reduction of the dextrose tolerance. These findings seemed to open up new possibilities regarding other glands. If removal of seven-eighths or nine-tenths of the pancreas may give rise to diabetes, it is conceivable that removal of similar fractions of "antagonistic" glands may partially or entirely check this diabetes. If so, we might then suppose, with the polyglandists, that human diabetes represents an absolute or relative over-function of the thyroid and adrenals; and just as Graves' disease is cured or benefited by reduction of thyroid tissue, so we should hope that diabetes might be benefited by reduction of thyroid and adrenal tissue. Experiments might deal with (A) total or (B) partial removal of these organs.

(A) Total removal of the adrenals is followed by such sudden death that the undertaking in this connection is useless. Total thyroidectomy has been performed by others in totally depancreatized animals; the results have been interesting; and in dogs with the type of diabetes which I have studied, total removal of the thyroid (leaving the parathyroids) appears as an attractive field of research. But total thyroidectomy would never be proposed as a cure for human diabetes; and as the purpose of this work has been primarily an application to clinical conditions, it was found necessary under existing circumstances to leave with regret the field of total extirpations, and limit the attempts to partial extirpations.

(B) Partial extirpations may include adrenal tissue or thyroid tissue alone; but the publications of Asher and Flack, and of Caro, seem to indicate the possibility of a mutual reënforcement between the thyroid and adrenals. For this reason it was hoped that specially marked results might be obtained from the removal of the greater part of the thyroid tissue together with the greater part of the adrenal tissue.

The experimental undertaking has been favored by the fact that my diabetic animals are able to live for months in reasonably good condition, and though severely diabetic, are able to withstand repeated operations practically like normal dogs. It is also possible to work with partially depancreatized animals which are not diabetic, but are close on the verge. Accordingly, a general inquiry into the polyglandular doctrine was undertaken, dealing with the influence of the thyroid and adrenals upon the carbohydrate economy of normal animals, upon the production of diabetes, and upon the cure or modification of this disease.

Adrenals.

In a series of dogs and cats of which the protocols will be omitted, it was determined that removal of one adrenal has no effect whatever upon the dextrose tolerance nor the diuretic behavior of dextrose, by subcutaneous tests. Also, the cats were subjected to starvation periods, and the nitrogen output was determined in each animal for periods with and without daily subcutaneous injection of 3 g. dextrose per kilo. There was no variation from the behavior of normal animals.

In a series of cats, various attempts were made to reduce the quantity of adrenal tissue much further. In this connection it may be noted that Moussu and Le Play (1) found hypertrophy of the fragment when only a portion of one adrenal was left. Crushing or ligating the adrenals, or injecting zinc chloride, caused death the same as removing them. When the glands were removed and distributed in the form of small grafts in the retrorenal connective tissue, death occurred as quickly as after simple epinephrectomy. Shiota proved that an adrenal ligated off but left in place loses its adrenalin within 24 hours. Martinotti found fibrosis of the adrenals, with persistence of nothing but a little cortical tissue, after ligature of the central veins of the adrenals. He refers to Vassale and Zanfrognini, who claimed that if the medulla were removed, leaving the cortex, the animals died with the usual acute symptoms; but if a trifle of the medulla were also left, they died only after 3 or 4 weeks, with anorexia, weakness, subnormal temperature and emaciation.

In confirmation of other authors, I was able to lift the adrenals from their bed and handle them without fatal result. In Cat 68, the right adrenal was ligated off and left in position. One month later, the left adrenal was similarly ligated and left; the cat died with the symptoms of epinephrectomy. Autopsy showed the left adrenal not much changed in gross appearance, but miscroscopically in necrosis and invaded by leukocytes. The right adrenal was replaced by scar-tissue, and microscopically no adrenal tissue could be found. The hope therefore that circulation through the capsule might preserve enough cortical tissue to maintain life was not fulfilled.

In Cat 72, eleven-twelfths of the left adrenal was removed, leaving a tiny fragment composed of both cortical and medullary tissue. Six weeks later, the right adrenal was removed, and the

cat died two days thereafter, with the symptoms of epinephrectomy. In this as in totally epinephrectomized animals, subcutaneous injection of dextrose to the point of glycosuria failed to modify the symptoms. Furthermore, it may be noted that the tolerance in such animals is not elevated; there is no evidence of an alleged over-function of the pancreas. At autopsy, the tiny fragment of the left adrenal was found apparently in good condition; it was not examined microscopically.

There were several other failures with very small fragments. The best success was in Cat 60, to be mentioned later.

Thyroid.

Dog 36.

Female mongrel, yellow, age one year. Weight 9600 g. In excellent condition.

March 11, subcutaneous injection of 12 g. dextrose per kilo in 20 per cent solution. Urine 30 cc., sugar 6.6 per cent.

March 17, weight 9400 g. Removal of more than seven-eighths of the thyroid, sparing all parathyroids as carefully as possible.*

The symptoms of thyroid deficiency became very noticeable. The lively animal grew sluggish and stupid, and the weight rapidly increased.

April 25, weight 12,450 g. Subcutaneous injection identical with that of March 11. Urine 20 cc. with 0.52 per cent sugar; later 7 cc., with 2.1 per cent sugar.

Cat 46.

Female; vigorous adult, with tendency to obesity. Was in the laboratory for 8 months, and used for various experiments, which determined the dextrose tolerance at different weights, and the nitrogen output in periods of fasting alone or with subcutaneous dextrose injections.

May 24, weight 3320 g. Removal of seven-eighths of each thyroid lobe, sparing the portions supposed to contain parathyroids.

The cat showed no positive evidences of hypothyroidism. The weight rose above 4400 g., but the tendency to obesity had already been noticed, and this weight had been equalled before.

* For topography of the parathyroids, see Kohn, also Halsted and Evans, and Alquier.

Possibly there was some increase of laziness. The fasting nitrogen values were found not diminished. It was of some interest to learn whether dextrose given subcutaneously would affect the nitrogen output any differently when most of the thyroid was gone; but the results were identical with those in normal cat (Chapter IV). Also, the dextrose tolerance was barely over the values previously obtained in this cat. Though high, it was not beyond the limits of variation which may be shown by a normal animal.

The conclusion from Dog 36 and Cat 46 is that the assimilative power for dextrose is not perceptibly altered by removal of such fractions of thyroid tissue as were found, in the case of the pancreas, to alter the assimilation in extreme degree. In the case of the dog, the quantity of sugar excreted after thyroidectomy, with the increased body-weight and marked signs of hypothyroidism, was only a trifle less than from the identical dose before operation. Renal permeability might account for much greater variations than this. After complete thyroidectomy, the results might perhaps be a little more positive. As previously stated, it is possible that the tissues in states like hypothyroidism and hypopituitarism do possess an increased power of utilizing sugar, but such power has never yet been demonstrated. Of the three conditions governing tolerance, mentioned in Chapter I, impaired absorption and impaired excretion might fully account for the apparent increase of tolerance; an acceleration of utilization is not as yet proved. It is possible that in these states, the absorption from the subcutis is altered less than that from the intestine, and by the subcutaneous method it may perhaps be possible to decide whether the actual utilization is increased. If not, the method of prolonged intravenous infusion may be available; and blood-sugar tests will be useful for control. For the present, it can only be noted that in Dog 36, hypothyroidism was not accompanied by an increase of dextrose tolerance.

Adrenals and Thyroid.

Cat 60.

In brief, the record is that of a cat from which seven-eighths of the thyroid tissue and eleven-twelfths of the adrenal tissue were removed, with no important departure from the normal in consequence. A summary of the protocol is as follows.

December 29, the right adrenal was removed.

January 12–17, the cat fasted with daily subcutaneous injection of 3 g. dextrose per kilo, then the fast was continued to January 22 without injections. The sugar tolerance and the nitrogen were normal.

On January 24, a test of emotional glycosuria was negative, but the same experience has been frequent with equally gentle normal cats.

January 25, five-sixths of the left adrenal was removed.

February 13–24, the cat fasted and received daily subcutaneous injections of 4 g. dextrose per kilo. Also April 7–21 was a fasting period without injections. On May 10 the dextrose tolerance was tested by a subcutaneous injection of 3 g. per kilo. May 16–22 was a fasting period with daily injection of 3 g. dextrose per kilo. Throughout the series, the nitrogen values and the dextrose tolerance were normal; no over-function of the pancreas was demonstrable.

On June 1, seven-eighths of the thyroid was removed. The cat seemed to become more sluggish, and the weight rose above the former limits.

June 27 to July 5 was a fasting period, with normal nitrogen values.

July 13–22 was a fasting period with daily subcutaneous injection of 3 g. dextrose per kilo. Nitrogen values were lower than in the preceding period, but no lower than in some of the earlier periods. The urine was free from sugar till a dose of 4 g. dextrose per kilo was given on July 21; this caused a glycosuria of 2.2 per cent, indicating a normal tolerance.

On August 6, emotional glycosuria remained absent even with 5 hours' tying. Lack of excitability is a simple explanation.

For further information concerning the sugar tolerance, on August 10 was given a subcutaneous injection of between 3 and 4 g. dextrose per kilo. A blood-test two hours later showed the high value of 0.452 per cent. Glycosuria was slight. The conclusion again is that an "increased function of the pancreas," corresponding to the reduction of thyroid and adrenal tissue, and manifested in an increased ability to utilize dextrose, is not demonstrable.

On September 16, the cat was bled to death from the carotid. The autopsy was negative. Qualitative tests indicated a normal content of glycogen in the liver. The first of the blood was

collected for sugar-determination; an exact result was prevented by an accident; but the estimation was sufficiently close to prove that the percentage was certainly within normal limits. All viscera were normal; in particular, the pancreas was not enlarged, and was fully normal to gross and microscopic examination. The thyroid fragments were as left at operation; there was no appearance of hypertrophy. Adrenal tissue was absent except the fragment on the left side. Here the condition was interesting, for it was found hypertrophied, so as to be about a third as large as a normal adrenal. Also, at operation a wedge had been left, consisting largely of naked medulla. At autopsy, it was found rounded off into a spheroid, and the cortex had apparently grown around to envelop the medulla, so that the appearance was like a small whole adrenal. Microscopically, the hypertrophy seemed to be limited to the cortex; apparently the medulla had not enlarged. The cells were normal in all respects except for a less regular arrangement than in the normal cortex. In this connection, reference may be made to Biedl [(3), p. 164] concerning authors who have found that naked medullary tissue, without cortex, is not capable of transplantation except in those species in which the medullary tissue normally lies free and uncovered.

Feeding and Injection.

The thyroid tablets here referred to are the U. S. P. preparation, by Parke-Davis, of 2-grain size, each tablet equivalent to 10 grains of fresh sheep thyroid.

Cats 46 and 47.

These two cats were starved from November 22 to December 10, while receiving four thyroid tablets daily. Toward the end, a trace of reducing substance appeared in the urine of each; it was not identified by any further tests. Starch-feeding in Cat 47 failed to increase the reaction, perhaps because of poor digestion of starch. As was mentioned in previous chapters, cats do not show hunger-glycosuria like dogs; they retain their assimilative power very well. But under the influence of combined starvation and thyroid feeding, it was noteworthy that the apparent tolerance could be decidedly lowered. In Cat 47, which reacted negatively to starch, doses as low as 1 g. dextrose per kilo by mouth produced glycosuria as high as 0.6 per cent. In Cat 47, a similar glycosuria was produced by subcutaneous injection of 1 g.

dextrose per kilo. But when the doses were increased to 3 g. per kilo, the excretion was practically the same as with 1 g. per kilo; the urine was diminished. Therefore the anti-diuretic and paradoxical laws of dextrose were maintained as usual.

On December 10, starvation was ended by placing each cat on a regular diet of 130 grams horsemeat and 20 grams fresh sheep thyroid. On December 13, with this diet, Cat 47 received a subcutaneous injection of 3 g. dextrose per kilo. The bladder was emptied by pressure at regular hours, and the urine record was as follows:

December 12, 136 cc., no sugar.
December 13, 140 cc., no sugar.
Injection as stated.
Evening urine 5 cc., moderate Benedict reaction.
December 14, 116 cc., very faint Benedict reaction.

Here as usual the excretion was trifling, and the urine was evidently diminished till after glycosuria was ended.

On the same date, Cat 46 received a subcutaneous injection of 3 g. dextrose and $1\frac{1}{2}$ mg. adrenalin per kilo. Under the combined influence of thyroid, adrenalin and sugar, the urine record was as follows.

December 12, 204 cc., no sugar.
December 13, 100 cc., no sugar.
Injection as stated.
Evening urine 8 cc., very heavy Benedict test.
December 14, 156 cc., moderate Benedict test.
Evening urine 44 cc., faint Benedict test.
December 15, 110 cc., no sugar.

In this case the quantity of dextrose injected was 6.6 g., while the total excreted was 7.97 g. In view of the usual summation of effects of glycosuric agencies, this excess of excretion over injection is not surprising. But the point to be noted is the oliguria which accompanied the heaviest glycosuria; only very slowly did the diuretic action of the adrenalin come to prevail over the anti-diuretic action of the sugar. This condition, under the combined influence of thyroid and adrenalin, is in sharp and decisive contrast with the flood of polyuria which follows the administration of dextrose in a diabetic animal. Here, as in diabetes, the sugar excreted is more than the sugar injected; furthermore the adrena-

lin is a diuretic; but dextrose nevertheless proves itself an antidiuretic. The experiment contributes further evidence that the diuretic action of dextrose in diabetes is not a simple matter of the quantity of dextrose excreted.

The experiment was ended at this point, and no attempt was made to demonstrate the dextrose paradox. But it could undoubtedly have been demonstrated that, although with this small dosage the excretion exceeded the injection, utilization is obtainable simply by increasing the dose of dextrose; and the more dextrose is given, the more will be utilized. In this respect also, the condition in this toxic glycosuria is the exact opposite of diabetes.

Cat 48.

This was a small vigorous female, with a normal weight of about 2300 g. Her dietary requirement was found to be about 125 g. meat. On this diet, between October 19 and November 14, a series of careful subcutaneous tests fixed her dextrose tolerance at a little over 4 g. per kilo.

After a short period of freedom, she was again caged and placed on this diet on November 19, weighing 2555 g., and the nitrogen excretion was followed till November 29, when her weight was 2620 g.

November 29 to December 14, the diet was 105 g. meat and 20 g. fresh sheep thyroid. The weight on December 15 was 2380 g., but the loss was due to diarrhea; the nitrogen analyses were made all during this period, but they showed a slight decrease, owing to the diarrhea. They served their purpose, however, of proving that in the glycosuria resulting from dextrose injections during thyroid feeding, the nitrogen excretion is not increased, as it is in diabetes.

There was no spontaneous glycosuria, and no symptoms resembling clinical hyperthyroidism. On December 1, feeding of 5 g. soluble starch produced no glycosuria.

December 5, feeding of $1\frac{1}{4}$ g. dextrose per kilo caused moderate glycosuria, *i.e.*, the tolerance was decidedly reduced; but the sugar-containing urine was only 40 cc., as opposed to an average daily output of 90–120 cc.

December 8, the same dose caused no glycosuria.

December 9, subcutaneous injection of 2 g. dextrose per kilo caused slight glycosuria and a diminution of urine, *i.e.*, the apparent tolerance was less than half normal.

December 10, subcutaneous injection of 3 g. dextrose per kilo caused hardly any greater sugar-excretion than the previous doses; *i.e.*, the paradoxical law was maintained.

December 11, a subcutaneous injection of $1\frac{1}{2}$ mg. adrenalin per kilo was given. The excretion was 1.825 g. dextrose. Thus, notwithstanding the lowered tolerance, the glycosuria (and diuresis) resulting from a combination of thyroid and adrenalin was within the usual limits.

Neither the sugar nor nitrogen values ever showed any diabetic tendency.

Dog 17 (see protocol).

On March 9, $\frac{4}{5}$–$\frac{5}{6}$ of the pancreas had been removed, and the tests on subsequent occasions had proved the dextrose tolerance to be low. Beginning May 13, fresh sheep thyroids were added to the regular diet of bread-and-meat mixture. At first a dozen glands were fed, weighing 45–50 g., but on May 16 the daily quantity was increased to two dozen large glands, weighing over 100 g. Carlson has noted the cardiac irregularity in dogs, which agrees with my experience; but in this animal the thyroids seemed to cause increased irregularity and weakness of the heart, and there was a definite increase of restlessness and excitability of the dog. There was also a steady loss of weight, even before diarrhea began, though the thyroids represented an addition of 100 g. to a diet on which the dog had been gaining weight since April 21. Also, a slight spontaneous glycosuria developed (the substance in the urine reduced Benedict solution and gave typical fermentation and osazone tests). On May 20, with existing glycosuria, the dog received a subcutaneous injection of 4 g. dextrose per kilo. The excretion was insignificant in comparison with the dose; it was no greater than this dog ordinarily showed from such a dose without thyroid. Also the anti-diuretic effect of the dextrose, as shown in the evening urine, was well marked.

May 22, the same dose was given by mouth. Glycosuria was no greater than without dextrose. Owing to the greatly increased drinking, diminution of urine was absent.

May 23, more than 10 g. per kilo of commercial glucose was given by stomach tube. Heavy glycosuria resulted; and on account of greatly increased drinking, and the diuretic action of impurities in the glucose, the evening urine was increased.

May 24, in order to control the unknown factors of May 22 and 23, the dog was fed 100 g. Kahlbaum dextrose immediately

after the morning catheterization. There was no tendency to vomit. Measuring of water showed that 570 cc. was drunk during the day; yet the evening urine, containing 4.56 per cent dextrose, was only 290 cc. in volume, as compared with 490 cc. for the next morning, when the glycosuria was negative.

Although the animal had a toxic glycosuria of thyroid origin, there was no tendency for this glycosuria to continue, and the tests based on the paradoxical law and anti-diuretic action of dextrose prove that the condition was not diabetes. A clinical application may be made as follows. Thyroid intoxication may produce glycosuria in any patient. If the pancreas is weak, thyroid like other forms of glycosuria is produced more easily. If diabetes is present, it is of pancreatic origin as always; the thyroid has no direct part in it.

The absence of any thyroid-pancreas "antagonism" is here demonstrated. The animal was predisposed to diabetes; diabetes might have been produced by removal of a very small portion of pancreatic tissue, or by weakening the functional power of the pancreas by the means indicated in Chapters XVII and XX, or by any other means. But diabetes was not produced by thyroid excess, even though the feeding was pushed to the point of toxic glycosuria. The conclusion is that the thyroid does not alter the pancreatic function, and has no direct part in the production of diabetes.

Operations Upon Diabetic Animals.

Dog 20; female; age 11 months; weight 5635 g.

December 7, removal of pancreatic tissue weighing 14.7 g. Remnant about lesser duct guessed roughly at 3 g. [evidently too high; remnant found at autopsy weighed 2.7 g.]. Diabetes gravis.

January 21, removal of left adrenal. No effect whatever upon the glycosuria, acetonuria or other symptoms. The urine on meat diet was regularly 600–700 cc., with 5–7 per cent sugar.

February 2, operation on right adrenal. Difficult adhesions were found. The adrenal was removed except a fraction guessed at $\frac{1}{4}$–$\frac{1}{6}$, with vascular supply supposedly preserved. The operation was ended at 4 p.m. At 5 p.m. the urine was 78 cc., with 3.3 per cent sugar. At 6 p.m. it was 22 cc., with 0.44 per cent sugar.

February 3, morning urine 25 cc., sugar-free. At 3 p.m., urine 7 cc., sugar a trace. A 5 p.m., urine 20 cc., sugar a trace. At 8 p.m., urine 35 cc., sugar 0.29 per cent. The condition in the morning had seemed to be good, but weakness became manifest during the day. Appetite was absent, thin diarrhea present; a little milk given by stomach-tube seemed to be excreted little changed in the feces. The temperature sank below 95 degrees.

February 4, temperature 94⁴. Dog too weak to stand. Scanty urine spoiled by mixture with feces. At 9:30 a.m., subcutaneous injection of 18 cc. 40 per cent dextrose solution. No improvement. At 10:45 a.m., vomited clear liquid and choked to death by aspirating it.

Autopsy showed left adrenal completely absent. Owing to confusion caused by the adhesions, the blood-supply of the small fragment of the right adrenal had been cut off; it was entirely necrotic. No infection anywhere. Tests of liver and muscles for glycogen were entirely negative.

The suppression of glycosuria after destruction of the second adrenal cannot be interpreted in a specific sense. Authors have shown that the liver-glycogen disappears within a few hours after epinephrectomy, and Gautrelet and Thomas have proved that the sympathetic mechanism is quickly disabled. Failure of sugar-production is therefore to be expected. But glycosuria is not a measure of diabetes. The epinephrectomy certainly did not restore any power of utilizing sugar; and without such restoration, the animal is just as diabetic as before; it has merely suffered an additional and fatal injury. Many authors bear witness to the cessation of glycosuria in consequence of inanition, from non-specific causes, even in totally depancreatized animals. The fact is attested by Minkowski (1), by Lepine [(1), pp. 359–62; also (2)], by von Noorden [(3), p. 561], by Pflüger [(16); a dog totally depancreatized by Witzel lived 2½ days without glycosuria]; and by Tiberti and Franchetti (1 and 2). In former chapters I have recorded similar results of dogs in which the entire pancreas was extirpated except a remnant, which suffered total necrosis; yet glycosuria was practically or entirely absent. A specific effect of the epinephrectomy in this case therefore cannot be claimed.

Dog 19.

The animal was made diabetic by partial pancreatectomy February 7.

March 21, seven-eighths of the thyroid was removed, sparing the parathyroids as carefully as possible. There was no effect whatever upon the glycosuria or other symptoms.

April 11, ligatures were placed about the left adrenal in such manner as to destroy three-fourths of it, leaving only the one-fourth about the hilum in communication with the vessels. The glycosuria was diminished for the first 24 hours, owing to weakness and fasting; when meat was eaten on April 12 the glycosuria promptly returned in full intensity.

April 21, removal of the right adrenal was proposed, but the weakened animal died as soon as the peritoneum was opened.

There was never any sign of specific influence upon the diabetes from the reduction of thyroid and adrenal tissue.

Remarks Concerning Experiments.

The preceding series might have been continued, and the procedures been made more radical. But the results as they stand sufficed to convince me that this idea, of which I had at first considerable hopes, is absolutely fruitless. In my opinion there is no antagonism or balance whatever between the pancreas and any other organs, or it is so slight as to be without practical importance.

As I have already shown, dogs may be brought so close to diabetes, that the removal of a fraction of a gram of pancreatic tissue will send them over the verge. Such animals are valuable test-objects. In them, it is possible to try whether any thyroid or adrenal excess is able to produce an effect equivalent to the loss of the smallest fraction of pancreatic tissue; or, if this fraction be first removed, it may be tried whether any reduction of adrenal, thyroid or other tissue is able to prevent diabetes. Errors of interpretation must be guarded against. Other organs may well modify the course of diabetes. An animal with diabetes levis, for example, is genuinely diabetic, and simple carbohydrate diet suffices to bring on diabetes gravis. It is conceivable that in such an animal, thyroid intoxication may produce glycosuria of diabetic character on meat diet, simply because of the metabolic strain, and the general injury which is felt most heavily by a weakened function. Here the thyroid intoxication is merely on a par with carbohydrate food; it does not produce, it merely aggravates the diabetes. The condition is comparable to that of

human patients who show diabetes with hyperthyroidism; the diabetes is from the pancreas nevertheless. There is a possibility, and an interesting one, that suitable hypophyseal operations may produce diabetes in suitably predisposed animals, and thus the association of diabetes with acromegaly may be illuminated. But such a result, if obtained, is best interpreted as an influence of the hypophysis, directly or through an internal secretion, upon the nervous system; it may almost rank with the production of diabetes by the piqûre. The best evidence is against the idea that the hypophysis furnishes any substance which is used directly in carbohydrate metabolism. Also, the suppression of glycosuria by cachexia is not to be interpreted as a cure of diabetes. If the diabetes is not too severe, it is conceivable that a total thyroidectomy may cause the glycosuria to diminish or cease, for two reasons; (*a*) in very mild cases, the simple slowing of metabolism and of absorption might throw a little less strain upon the pancreas, and thus be the equivalent of a restriction of diet; (*b*) a fatal cachexia may be produced, in which glycosuria ceases because of weakness and metabolic derangement. In all such cases, it should be clearly recognized that the diabetes is not cured; the animal has merely suffered two injuries instead of one, and is worse off than before. Diabetes is solely and invariably a disease of the pancreas. No disorder of any or all other glands can either produce or prevent it.

In Conclusion.

The polyglandular doctrine has consisted from the first of ingenious but unfounded speculations. Its authors must be given credit for the valuable experiments with which they have enriched medical knowledge, and especially for the able clinical studies by which they have pointed out the important differences between human diabetes and that which is produced in dogs by the methods heretofore employed. The doctrine, however, is arbitrary, confusing, and self-contradictory. It has gained wide acceptance not so much from positive merits of its own, as from the seeming absence of any other satisfactory explanation of diabetic phenomena. The following points may be noted.

1. The principal basis of the doctrine lies in superficial comparisons between gross, non-specific phenomena such as glycosuria and increased nitrogen excretion. But these are effects which

may result from many different causes; and fuller knowledge indicates that adrenalin glycosuria is of different nature from diabetic glycosuria, and the increased nitrogen excretion of thyroid intoxication is of different nature from that of pancreatectomy.

2. Even if the doctrine should be accepted in its entirety, it serves no purpose. In experiments, the diabetes resulting from total pancreatectomy is indeed not a perfect imitation of human diabetes, but no manipulations of any or all other glands have given anywhere near as satisfactory an imitation. Clinically, it will probably be conceded by all that if human diabetes were regularly attended with visible specific lesions of the pancreas, as of the kidney in Bright's disease, this polyglandular hypothesis would never have been uttered. But since, along with a normal or approximately normal pancreas, the typical diabetic autopsy shows also normal thyroid, parathyroids, adrenals, hypophysis and other organs, it is evident that the incrimination of these various organs contributes nothing whatever toward clearing up the real difficulties in the understanding of diabetes.

3. The doctrine is out of harmony with facts. There is no evidence for the existence of an adrenal-excess except in relation with certain demonstrable changes in the adrenals, or symptoms such as hypertension; adrenalin glycosuria without other symptoms than the glycosuria is unknown. Likewise, there is no such thing known, as hyperthyroidism without thyroid enlargement and symptoms of thyroid intoxication. All these signs and symptoms of adrenal and thyroid excess are absent in typical diabetes. And if it be supposed that the over-function of the adrenals and thyroid is only relative and not absolute, and that insufficiency of the pancreas is the essential condition, then we have come back to the pure pancreatic theory, and there is no object in assuming a perversion of function on the part of these other glands which is out of harmony with the known facts.

4. The perception of the differences between human diabetes and that following total pancreatectomy was an important advance step; but the authors then went astray by seeking the explanation in the different functions of the pancreas and other organs, instead of in the different functions of the pancreas itself. As previously mentioned, it is possible by suitable pancreatic operations to demonstrate these different functions. In particular, the method of partial pancreatectomy, which I have described, gives a type of diabetes which differs in important respects from that following

total pancreatectomy, and is a better reproduction of the human disease than has been obtained by any other means.

The understanding of pancreatic insufficiency as the sole and invariable cause of diabetes gives a unified conception of the disease, and furnishes a definite basis for measures looking toward a causal therapy.

CHAPTER XX.

THE LIVER AND DIABETES.

In hypotheses concerning the etiology and mechanism of diabetes, from the earliest times to the present, the liver has generally played a prominent part. Its importance in general metabolic processes, and as a storehouse of glycogen, and as a regulator of the sugar of the blood, have naturally pointed toward it in connection with a disease in which metabolic processes and the economy of glycogen and sugar are so markedly disturbed. Probably above everything else, the ignorance concerning the liver, coupled with the ignorance concerning diabetes, has created the tendency to bring the two into relationship.

As is well known, Claude Bernard looked upon diabetes as a circulatory disturbance of the liver. He considered the result of his piqûre to be a temporary diabetes, and explained it as a vasomotor disturbance; the increased blood-flow through the liver produces supposedly an increased contact between glycogen and ferment, and thus causes an accelerated formation of sugar. He drew support for this view from a wide variety of observations; the low glycogen content of fœtal livers was explained by the peculiarities of the fœtal circulation; the stability of glycogen in hibernating animals was similarly interpreted; likewise the possibility of preventing puncture-glycosuria by ligation of the blood-vessels of the liver, or by section of the spinal cord. The large hyperemic liver of diabetes was also looked upon as confirmatory; and furthermore Bernard [(3), p. 355] recorded a case of diabetes in which glycosuria disappeared with the onset of cirrhosis of the liver.

Seegen [ref. by Bernard (3), p. 446] also viewed diabetes as an increased formation of sugar in the liver, but believed the disturbance to be nervous instead of vasomotor. Pavy [(2), p. 112] held the opinion that diabetes depends upon the failure of the liver to hold back the sugar derived from the food. Chauveau and Kaufmann in their hypotheses attempted to bring into relation the diabetogenic rôle of the nervous system, pancreas and

liver; and the last organ held an important place in their doctrines. Schiff and others have proved that removal of the liver prevents glycosuria from piqûre. As was noted in Chapter XII, there are several forms of glycosuria which persist after removal of the liver. But diabetic glycosuria is not one of these. Marcuse in particular proved that removal of the liver prevents glycosuria in frogs after pancreatectomy. Upon Marcuse's work, Pflüger (13) set up the dictum, "Ohne Leber kein Diabetes." This dictum has stood practically without question; it is frequently referred to, and is used recently by Frank and Isaac (4). Conclusions have been drawn from perfusions of diabetic as compared with normal livers [see Zuelzer (4), Hinselmann (1), Lattes (1)]. The polyglandists have universally designated the liver as the seat of diabetic disturbance, in relation with the fact that the liver is also the point of attack of adrenalin. As a matter of fact, Pflüger's dictum is without justification. It is based only upon the confusion between diabetes and glycosuria. A depancreatized dog whose glycosuria has stopped because of weakness is just as diabetic as he was before; the same is true after removal of the liver. It would be just as reasonable to drain off a frog's blood; its tissues will still show signs of life, but there will be no glycosuria; and the cry may then be raised, "Ohne Blut kein Diabetes." The truth is that a depancreatized animal is always diabetic; carbohydrate utilization and other functions depending upon the pancreas are prostrated; and the idea that removal of the liver cures the diabetes or restores the lost pancreatic function is preposterous. If the liver were a dispensable organ like the spleen, the thought of curing human diabetes by its ablation would still be absurd; what is required is a restoration of the lost pancreatic function, not the infliction of an added metabolic injury.

According to Lepine [(1), pp. 488–90] the liver is frequently increased in size in diabetes. Von Noorden [(1), p. 194] states that in many diabetics a moderate enlargement of the liver can be demonstrated even during life, and slight tenderness and hardness of the organ are generally present at the same time. Lately Hirschfeld (3) has particularly emphasized the enlargement and tenderness of the liver, and drawn etiologic deductions for some cases. In diabetes following total extirpation of the pancreas, a large fatty liver is common; and Sandmeyer noted the same change in his type of diabetic dogs. Pflüger [(13); also (1),

p. 495] was particularly impressed by the appearance of the liver in the latter type of animals; the impression was of a wasting of the entire body as if from extreme starvation, while the liver remained large out of all proportion to the general body-weight. Naunyn (p. 56 and elsewhere) has credited the existence of a "liver-diabetes," *i.e.*, occasional cases in which disease of the liver is a factor in producing diabetes. So far as a specific etiologic agency of the liver is concerned, this view cannot be accepted, and is not accepted by any other authorities. But disease of the liver may be the cause of, or associated with, disease of the pancreas, and the origin of the diabetes is thus explained, as is clearly pointed out by Lepine [(1), pp. 427–31].

B. Fischer first observed an increase of Kuppfer's reticular fibrils (Gitterfasern) in the livers of diabetic patients. Roessle noted macroscopically the large size, hyperemia, and firmness of diabetic livers, and two characteristics microscopically, (1) filling of Kuppfer's stellate cells with fat, (2) thickening of the reticular fibrils and their metaplasia into collagenous bundles. E. Schmidt studied the reticulum in normal and pathological livers (not in diabetes), finding it increased in cirrhosis, etc. Herxheimer (1*A*) also studied a series, including diabetic livers; and considered that though the reticular thickening is not limited to diabetes, it may be a useful diagnostic point along with others. As the cause of the reticular proliferation, authors suggest hyperemia or a slight toxic irritation as in cirrhosis; and as the cause of the fatty deposits in the Kuppfer cells, the lipemia. The occurrence of glycogen in the nuclei of the liver cells was previously mentioned. Omi found that the liver-extract from depancreatized dogs splits salicin more actively than that from normal dogs. In general, therefore, various slight changes of the liver have been observed in diabetes, but none of them are specific.

Concerning another condition in which hepatic changes are associated with diabetes, the following quotation may be taken from Futcher [(1), pp. 756–57].

"At this point also must be mentioned the interesting group of cases of 'bronze diabetes,' occurring as a late manifestation of the remarkable affection known as hæmochromatosis. The latter condition is characterized by a peculiar pigmentation of the skin and viscera, associated with a form of hypertrophic cirrhosis of the liver and extensive sclerotic changes in the pancreas, and accompanied in the late stages by a persistent glycosuria. Hanot and Chauffard first described these cases in 1882, and, in 1886, Hanot suggested the name *diabète bronze* for this type of diabetes, and,

as he considered the liver changes secondary to the diabetic condition, he gave the name *cirrhose pigmentaire diabétique* to this form of cirrhosis. The true nature of the affection was first revealed in 1889 by von Recklinghausen, who described the disease under the name of hæmochromatosis. He showed that the pigmentation of the skin and viscera is due to the deposition of an iron-containing pigment, hæmosiderin, and a non-iron-containing pigment, hæmofuscin, in the tissues.

"According to the latest conception of the disease, hæmochromatosis is to be considered as a primary affection of the blood in which the red cells are made more vulnerable, causing them to disintegrate more readily and to give up their hæmoglobin. The hæmosiderin possesses a brown color and is deposited mainly in the cells of the liver, pancreas, lymphatic and sweat glands. The hæmofuscin, on the other hand, is finer, of an ochre-yellow color, and is present in the smooth fibres of the stomach, intestines, blood- and lymph vessels, and occasionally in those of the urinary bladder, ureter and vas deferens. Hess and Zurhelle have recently made very careful studies of two cases of 'bronze diabetes,' that is, two cases of hæmochromatosis which had advanced to the diabetic stage. As a result of their chemical and histological studies they incline to the view that the cirrhosis of the liver and the formation and deposition of the pigment are dependent upon some common cause. They hold that some toxic substance, possibly alcohol, causes disturbances in metabolism which bring about the above changes. A lipæmia, which was present in one of their cases, is explained in the same way. Their investigations also go to show that a sharp distinction between hæmosiderin and hæmofuscin cannot be made. They claim to have found them side by side in the same cell with gradual transitions from one into the other. The hæmoglobin of the blood is in all likelihood their common source. As a result of the local deposition of the pigment in the liver and pancreas, a chronic interstitial inflammation occurs, producing in the case of the liver, a hypertrophic pigmentary cirrhosis, and, in the case of the pancreas, an interstitial pancreatitis of a pigmentary type. In the early stages or early years of this affection sugar does not appear in the urine, and it is only when the changes in the pancreas become so advanced that presumably the islands of Langerhans are largely or completely destroyed that diabetes develops. Whenever hæmochromatosis, either with or without diabetes, is suspected, the correctness of the diagnosis *intra vitam* will be made much more probable by removal of portions of the pigmented skin and the finding of iron-containing pigment in the cells of the sweat glands, by the potassium ferrocyanide test, and of the ochre-yellow hæmofuscin in the muscle fibres of any blood vessels that may be present."

In this type, therefore, as in all others, the cause of the diabetes is in the pancreas.

Other opinions concerning the rôle of the liver in diabetes are too numerous in the literature to permit full review. Rosenfeld (5, 6, 7) places the liver in the center of normal and diabetic metabolism. Ramond considers that in addition to the pancreas, the liver is a determining factor in diabetes. Funck has attributed great importance to the liver. Gilbert and Carnot [ref. by Lepine (1), p. 684 and von Noorden (1), p. 262] have even attempted to treat diabetes with liver preparations. Gigon has

attributed the benefit of opium in diabetes to its action upon the liver. Schlesinger (1) has attributed to the liver the glycosuria resulting from ligation of the thoracic duct, and this view is to be preferred to that which considers it to be due to an effect upon the pancreas. Heger and De Meyer have claimed to restore the lost power of glycogen-formation in the post-mortem diabetic liver by adding pancreas-extract to the blood with which it is perfused. Freund and Popper have reported increased formation of glycogen in the liver when pancreas extract was added to dextrose solutions injected intravenously. The results are perhaps due to coincidence. Porges and Salomon, supported by von Noorden, have supposed that by excluding the liver they could demonstrate that the power of the muscles of a diabetic animal to burn sugar is undiminished; thus the sole seat of the abnormal processes in diabetes is referred to the liver. Objections to their conclusions were stated in Chapter VII. The suggestions of Neubauer (4) have also been discussed heretofore. As previously mentioned, Hedon (13) has claimed different results in transfusion experiments, according to whether pancreatic-vein blood was received into the peripheral or into the portal circulation of a depancreatized animal. It is indeed possible that the liver, as an active metabolic organ, may have a specially great need for pancreatic amboceptor and therefore be provided with the richest supply of it, and the drainage of the pancreas into the portal circulation receives its most plausible explanation on this basis. But Hedon's experiments cannot be considered as proof that the internal secretion of the pancreas must be received into the portal circulation in order to be fully effective, for the following reasons.

1. According to this idea, the Eck fistula should cause diabetes. But it does not.

2. Carlson and Drennan found diabetes prevented in pregnant animals by the internal secretion from the young *in utero*. This secretion could not have entered the portal circulation directly.

3. Forschbach proved that parabiosis prevents diabetes. Here the internal secretion from one animal does not enter the portal circulation of the other.

4. Subcutaneous pancreatic grafts have been proved to prevent diabetes when the pedicle was cut, and when therefore the secretion was not received into the portal circulation.

In all the above experiments, the diabetes was actually prevented, as opposed to the results with transfusion into the portal vein, where there was merely a temporary diminution of glycosuria and the blood-sugar still remained high. The portal transfusion results are therefore best interpreted on the assumption that the toxic effect of the foreign blood, which was demonstrated in the case of the kidneys, is here concentrated upon the liver, so that the sugar-forming function suffers.

Pflüger, a firm believer in the importance of the liver, prepared [(1), p. 398] a list of the different known functions of the hepatic cell, and contrasted it with Aristotle's maxim that an instrument to be perfect must serve only one purpose. But, on the one hand, it is probably as erroneous from a certain standpoint to look upon a cell as a single entity, as it is to look upon an entire animal as a single entity; and, on the other hand, probably most of the cells of the body perform just as long a list of varied functions as that detailed by Pflüger for the hepatic cell. The present trend of research is toward a reduction of the supposed importance of the liver; the former ideas concerning its practical monopoly of some of the most important processes of metabolism are being shattered. Its predominant rôle in carbohydrate metabolism has been disputed by a series of researches; Külz (3) and others have proved that the muscles can form glycogen without the aid of the liver; the notions of alimentary glycosuria starting from Ginsberg's work have been overthrown; Verzar (2) and others have proved that the liver is not necessary for the burning of carbohydrate, and this view is confirmed by the Eck-fistula experiments. The formation of uric acid is not confined to the liver. Bile-pigments can be formed in other organs besides the liver [Hammarsten, p. 416]. The idea of a protein synthesis in the liver has been disproved, for example, by Abderhalden and London's Eck-fistula experiments and similar work; and the subject has been placed on a new basis by the researches of Folin and Denis (1, 2, 3). It had previously been acknowledged that urea can be formed elsewhere than in the liver; but Folin's view reduces protein metabolism to its simplest and most reasonable basis, viz., that amino-acids are carried by the blood through the liver, and distributed to the muscles and other tissues which require them for food; that these tissues use the amino-acids and transform them into urea and other waste-products without aid of the liver. By inference, and in combination with other evidence,

this demonstration militates strongly against the opinion that the metabolic disturbance in diabetes is a process confined solely to the liver.

In this connection also, some of the numerous experiments with the Eck fistula should be reviewed. This anastomosis between the portal vein and inferior cava was devised by the surgeon after whom it is named, as a surgical relief for the symptoms of portal stasis in cirrhosis of the liver. With the methods of that time, the operation was found too dangerous in animals to justify its use in human patients; but the brilliant conception was seized upon by the physiologists. The paper of Hahn, Massen, Nencki and Pawlow contains a classical research with this method. Glycosuria was never observed in such dogs, but sometimes albuminuria. Complex nervous phenomena on meat diet were the most striking feature, consisting in change of disposition, blindness, tetanus, coma, loss of pain-sense with retention of consciousness, etc. These symptoms were attributed by the authors to poisoning with carbamic acid. If ligature of the hepatic artery were performed along with the Eck operation, the dogs died in coma within 40 hours maximum, generally within 12–15 hours.

Rothberger and Winternitz verified the work of Pawlow and his pupils, but found the nervous symptoms not due to carbamic acid. Some dogs show the symptoms without meat diet; others show no symptoms even on heavy meat diet. Differences in the size of the fistula or the collateral circulation, proposed by Pawlow as an explanation of the varying results, were found to be not responsible.

De Filippi (1 and 2) studied the carbohydrate metabolism in Eck-fistula dogs, with results which have been previously mentioned. Starch diet never produced glycosuria. The tolerance of levulose was markedly reduced, but that of dextrose only slightly. Such a dog may show the muscle-glycogen-content characteristic of an over-nourished dog, and the liver-glycogen-content characteristic of inanition. The author concluded that the muscles form glycogen independently, and that the function of the liver is neither specific nor indispensable for normal carbohydrate metabolism.

Hawk (1), studying the toxic phenomena, came to the following conclusions.

(1) The Eck fistula may or may not result in toxic symptoms when the dogs are on meat-rich diet. Some cases were free from symptoms when post mortem showed tight ligature of portal, ample fistulous opening, and no collateral circulation. (2) Animals failing to show toxic symptoms on meat alone showed them when Liebig's extract was added to meat. (3) Toxic symptoms consisted in ataxia, tetanus, catalepsy, paresis, complete anæsthesia, total blindness and deafness; generally death, sometimes recovery on change of diet. (4) Toxic symptoms were absent after meat-free diet, even when Liebig's extract was added to the diet. (5) Feeding or intravenous injection of sodium carbamate did not produce the toxic phenomena. (6) Feeding or injection intravenously of sodium carbamate in normal dogs on meat diet produced no toxic symptoms, even if Liebig's extract were also fed. (7) Glycosuria did not follow carbohydrate food after Eck fistula. (8) Liebig's extract never caused albuminuria in fistula dogs. (9) After fistula, sometimes a period followed during which dog was very nervous, restless and irritable. (10) Fistula invariably caused marked loss of weight. (11) Meat was refused by fistula dogs after recovering from the toxic symptoms caused by meat. (12) The general conclusion is that something in Liebig's extract is toxic with meat, but harmless when there is no meat in the diet.

Macleod (3) established Eck fistulas, and later ligated the hepatic artery. Hypoglycemia was found to result.

Fischler (1, 2, 3) described acute degenerations in the liver and fat-necroses in consequence of the Eck fistula. He concluded that pancreatic injury may cause both fat-necrosis and liver-degeneration, with death; but that such results can be prevented by preliminary injections of trypsin. He also (3) drew a distinction between the symptoms of meat-intoxication and of liver-degeneration in these dogs. The meat-intoxication is said to be relieved by large injections of saline solution, which dilute the poison; but the condition is supposedly an alkalosis, due probably to ammonia not neutralized by the liver; it is relieved by acids.

Michaud found that the Eck fistula prevents adrenalin glycosuria; but when a fistula-dog receives 100 g. dextrose by mouth, the blood-sugar behaves as in a normal animal, *i.e.*, remains normal or increases within normal limits.

Bernheim and Voegtlin have recently confirmed the toxic effects of meat diet in Eck-fistula dogs; but they find that when bones are mixed with the meat, the dogs do well, and they suggest some specific influence of the calcium. On mixed diet, these dogs live indefinitely, gain weight, and show nothing abnormal in strength, liveliness, sexual function, etc. The carbohydrate tolerance is only slightly lowered. Bile formation is so markedly diminished that the common bile duct can be ligated and resected,

yet jaundice remains absent and the excretion of bile pigments and acids in the urine is very slight; the result is explained by the diminished blood-flow through the liver, since the bile-pigments are normally derived from the hemoglobin of broken-down erythrocytes. The normal path of cholesterin excretion is blocked by tying the bile-duct; no cholesterin is found in the feces or urine, and its fate is unknown. The authors consider that they have shown the compatibility of the Eck fistula with well-being on mixed diet, and confirm the opinion by reference to a human case of occlusion of the portal vein. They consider that this operation will before long be performed in human patients for the purpose originally intended by Eck, namely, the relief of portal stasis in hepatic cirrhosis. They refer to Bier as having already opened the abdomen in two such patients with the purpose of performing an Eck fistula, and being prevented by adhesions, but planning to do it in the future. Vidal in France and surgeons in Italy are said to have the same purpose in view.

Experimental.

Though existing evidence is against a specific rôle of the liver in diabetes, it seemed to me that the possibility should not be too lightly dismissed. There is the fact, for example, that in certain lower vertebrates a single organ, the hepatopancreas, takes the place of the two separate glands; and it is conceivable that in higher species the two organs still preserve some community of function. Hirsch (1) had the idea of a normal interaction between a substance furnished by the pancreas and another furnished by the liver. Mention has been made of Hedon's idea, that the pancreatic internal secretion is most effective when introduced into the portal circulation. The spleen, according to Asher and Grossenbacher, Pugliese (2), and Vogel, is an organ for retaining and giving back to the organism the iron that is set free; and this may be one reason why the spleen should drain into the portal circulation. The adrenals are in connection only with the systemic circulation, therefore so far as anatomical evidence goes, it speaks for their relation with the systemic smooth muscle, and somewhat against their alleged normal specific relation with the liver. The question remains whether there is any special reason why the pancreas should drain into the portal circulation. One possibility that has never been ruled out is that the pancreas furnishes an internal secretion, and that the liver either uses or

completes this secretion; that unless the liver makes proper use of this substance, or changes it into the finished form, the substance is useless for the rest of the body, and diabetes results. The substance needed by the body is thus not merely a pancreatic secretion, but a pancreato-hepatic secretion. In this case a certain disorder of the liver might produce a result practically identical with disease or extirpation of the pancreas; in the former event the specific substance would lack its hepatic element, in the latter event it would lack its pancreatic element; but the effect on the body would be similar. Extirpation of the liver does not rule out this possibility, because of the prostration. Many cases of diabetes might then be explained in conformity with Bernard's belief, viz., as a disordered nervous or circulatory condition in the liver; and the various types of the disease and the observations of functional or organic changes in the liver might thus be accounted for. The hypothesis is almost certainly contrary to fact, but stands as a possibility unless disproved.

For the experimental approach to this general problem, two methods in particular seemed to offer the greatest promise: (1) the increase of the supply of arterial blood to the liver; (2) the occlusion of the portal vein.

1. Increase of the Supply of Arterial Blood to the Liver.

As previously mentioned, Bernard's explanation of the glycosuria resulting from piqûre was the simple increase of blood-flow through the liver. Though most authors now take a different view [Chapter XVII], Wertheimer and Battez still uphold the pure vasomotor hypothesis. Bernard [(3), p. 451] refers to the belief of Pavy, that the *arterialization* of the liver-blood is what produces the acceleration of sugar-production, and that the simple injection of *arterial* blood into the portal vein suffices to produce glycosuria. Bernard dismissed the claim as of little importance, because many substances may produce glycosuria on injection into the portal vein. But here Homer nodded; it is not a question of other substances; and if Pavy's claim of the effect of arterial blood is correct, it may conceivably be an illuminating fact in connection with the known hyperemia of many diabetic livers. Jardet and Nivière have stated that the direct transfusion of arterial blood from one rabbit into a mesenteric vein of another rabbit gives rise to glycosuria. Lepine [(1), p. 332] was unable

to confirm the statement. Arthaud and Butte observed glycosuria after ligation of the splenic and right gastro-epiploic arteries; the explanation that it is due to increase of the arterial blood-supply to the liver does not necessarily hold, for it might be caused by the nervous injuries. Schiff [ref. by Wertheimer and Battez (3), p. 364] claimed that ligation of the afferent renal veins in the frog, by increasing the blood-flow through the liver, produces glycosuria. Langendorff [ref. by Wertheimer and Battez] repeated the experiment with negative result. In general, we may conclude that nervous irritation is one possible explanation of all the above examples of glycosuria.

A series of experiments was accordingly undertaken to throw light upon the influence of a varying blood-supply to the liver. Authors state that ligature of the hepatic artery is fatal in rabbits, but in dogs may be performed with impunity, owing to free vascular communications.

Dog 38; female; age 2 years; weight 5–6 kilos.

June 14, subcutaneous injection at 1 p.m., of 10 g. dextrose per kilo in 80 per cent solution. Urine at 4:30 p.m. 20 cc., with 0.45 per cent sugar; next morning 60 cc., with faint sugar.

June 30, hepatic artery with its nerve-plexus cut between ligatures.

July 11, subcutaneous injection as on June 14. Urine at 4:30 p.m. 65 cc., sugar-free; next morning 115 cc., with faint sugar. The tolerance thus appeared a trifle higher than before, but the difference is within the limits of accidental variations.

July 17, subcutaneous injection of 12 g. dextrose per kilo. Urine at 4:30 p.m. 45 cc., with 0.4 sugar; next morning 260 cc., sugar-free.

August 2, removal of pancreatic tissue weighing 13.7 g. Remnant communicating with main duct estimated at 2 g. (slightly more than $\frac{1}{8}$). Diabetes levis ensued, as in a normal animal.

September 14, removal of 0.5 g. additional pancreatic tissue, followed by typical diabetes gravis.

It is concluded therefore that ligation of the hepatic artery does not lower the dextrose tolerance, and does not render a dog either more susceptible or less susceptible to diabetes.

From the time of Bernard it has been known that ligation of both the hepatic artery and portal vein prevents glycosuria from

piqûre. I am not aware that the effect of ligating them individually has been tried.

Cat 18; female, maltese; weight 3180 g.

August 3, 3 p.m., under ether, hepatic artery doubly ligated, sparing nerve-plexus as carefully as possible. Bladder emptied by pressure; urine sugar-free. Immediately thereafter, piqûre. 10:30 p.m., urine 48 cc., dextrose 2.8 per cent.

August 4, noon, urine 10 cc., sugar-free. Afternoon, death. Autopsy negative. Puncture accurate; artery occluded.

Cat 90; male, gray and white; weight 4250 g.

September 12, 4:30 p.m., under ether, portal vein ligated. Bladder emptied by pressure; urine sugar-free. Immediately thereafter, piqûre. 7:30 p.m., found dying. Urine 20 cc., dextrose 5.9 per cent. Autopsy negative except deep congestion of portal tract. Puncture accurate, vein occluded.

In a number of dogs and a few cats, I have ligated the portal vein or hepatic artery, and have never once seen glycosuria after the operation. Even in Dog 38, in which the hepatic plexus was also cut, there was no glycosuria. It is therefore reasonably certain that the heavy glycosuria in the above instances was the result of the piqûre.

Evidently, if the hyperglycemia from piqûre is a vasomotor phenomenon at all, the hyperemia is effective either through the hepatic artery alone or through the portal vein alone. The way is therefore paved for the following experiments.

Dog 68.

Female; mongrel; age 2 years; weight 8950 g.; in excellent condition on full diet.

June 21, afternoon, under ether, spleen removed, and splenic artery and vein anastomosed by suture. Good union obtained, without leak or obstruction; splenic and portal veins distended and pulsating. Dog recovered full liveliness promptly thereafter.

11 p.m., urine 160 cc., pale straw, sp. gr. 1012, slight Benedict test, no albumin. Dog drinks and retains 100 cc. mk. Hungry.

June 22, 8 a.m., urine 85 cc., pale straw, 1016, slight Benedict, no albumin or bile.

9 a.m., temperature 102⁶. Given 100 cc. 25 per cent glucose solution by stomach-tube.

11 a.m., urine 125 cc., water-pale, 1003, dextrose 1.1 per cent.

12 m., urine 85 cc., water-pale, 1002, slight Benedict. Ate 150 g. lean meat.

12:30 p.m., subcutaneous injection of 55 cc. 80 per cent dextrose solution (5 g. per kilo).

5 p.m., has not urinated.

June 23, temperature 103⁴. Urine 280 cc., amber, acid, 1020, faint Benedict.

June 24, temperature 105. Urine 480 cc., amber, 1020, sugar-free.

June 27, death, shown by autopsy to be due to gangrene of omentum from insufficient blood-supply. The gangrenous portion surrounded the anastomosed vessels, and these were black and thrombosed. Viscera entirely negative. Urine free from sugar and albumin to the end.

Dog 60.

Male; old; bull and mastiff mongrel, with perineal hypospadias for catheterization. Received June 24 in poor condition, weighing 17,870 g. Fed exclusively bread and soup, which he ate in enormous quantity, so that on July 21 he was fat at a weight of 28,000 g. A final hearty meal of bread and soup was given on the evening of July 20 and finished before morning. Urine always sugar-free.

July 21, 2:15 p.m., bladder emptied. Spleen and most of great omentum amputated, and splenic artery and vein anastomosed, without leak or obstruction; splenic and portal veins distended and pulsating. All the accessory details of the operation were left till after the anastomosis, and were then done leisurely, so that for more than half an hour the anastomosis was known to be effective, without sign of stoppage when the abdomen was closed.

5 p.m., urine 595 cc., straw, acid, 1022, sugar, albumin, bile, acetone and diacetic negative.

5:45 p.m., 96 cc., 1017, negative as before.

8 p.m., 50 cc., 1030, as before.

10 p.m., 350 cc., consisting to unknown extent, perhaps wholly, of liquid feces. No sugar.

Drank and retained a total of 600 cc. water since operation.

July 22, 9 a.m., temperature 102[6]. Urine 195 cc., deep amber, acid, 1042; strong odor of normal dog urine; nothing abnormal in tests. Dog acts well and lively. Drank 50 cc. milk; refused water.

5 p.m., temperature 102[3], urine a few drops, dark amber, acid, sugar and albumin negative. Dog drank a pint of milk; would take meat, but not permitted.

July 23, 9 a.m., temperature 103[5]. Urine 342 cc., deep amber, acid, 1029, nothing abnormal. Dog drank over a pint of milk; allowed to take a little bread and soup.

1 p.m., 100 cc. 20 per cent dextrose solution given by stomach-tube.

4 p.m., urine 225 cc., 1030, negative. Given by stomach-tube 350 cc. solution containing 80 g. dextrose.

5 p.m., temperature 103[6]. Urine 110 cc., acid, 1008, nothing abnormal. The excessively strong dog-urine odor was notable in all specimens.

July 24, 9 a.m., temperature 104[8]. Urine 675 cc., yellow, acid, 1011, all tests negative. Dog lively and playful in spite of temperature. No food given.

5 p.m., urine 850 cc., amber acid, 1012, negative as usual.

The further record may be summarized as follows. The urine returned to normal quantity, though the quantity was always rather high and the specific gravity rather low (mostly about 1020). Appetite was very poor, and weight was progressively lost, though the dog was always lively and apparently strong. There was a constant thin black diarrhea. The temperature was irregularly febrile, varying from 102 to 104[6]; it proved to be due to infection, but this, like all the other details, was carefully followed because of the question whether it might be due to the disorder of hepatic circulation.

Death occurred August 7, and was found due to peritonitis, resulting from the breaking of an abscess in the splenic region. This involved the site of anastomosis, which could not be found at autopsy; the vessels had sloughed, and were blocked by thrombosis centrally. The viscera were all apparently normal except the liver, which was riddled with large and small abscesses. The walls of the portal vein were greatly thickened.

Remarks.

The exact duration of effective anastomosis is not known, but may safely be assumed to be at least several hours. Gangrene

or infection spoiled the opportunity for extended observation of such a circulatory anomaly.

The polyuria in both animals after operation, in contrast to the usual post-operative oliguria, is open to question as to interpretation. It might be a nervous or a special metabolic phenomenon; or, as mentioned below, simple increase of pressure in the portal vein may perhaps under some conditions be a cause of polyuria.

Spontaneous glycosuria was absent or insignificant. In Dog 68, tests showed the dextrose tolerance to be lowered, but dextrose was plainly not a diuretic. Notwithstanding the intense arterial hyperemia of the liver, an effect like that of piqûre was not obtained. The results of these two experiments are not decisive; for polyuria occurred, and it might be possible that glycosuria was absent on account of sudden disappearance of liver-glycogen. For example, it is questionable if the glycogen-loss following epinephrectomy is anything specific; Lepine [(1), p. 127] states that ligature of the hepatic artery is followed by total loss of glycogen within a few hours; Grünwald has found that any serious bilateral renal operation causes disappearance of liver-glycogen; and there is also the observation of Laves that muscle-glycogen rapidly diminishes after extirpation of the liver. However, these two experiments, coupled with the others in which piqûre produced intense glycosuria after ligation of the hepatic artery and portal vein respectively, contribute somewhat to the belief that the effect of piqûre is more than a simple vasomotor disturbance.

It is regretted that there appeared to be no opportunity of continuing this series of experiments, especially with dogs predisposed to diabetes by partial pancreatectomy. It seems that the authors who originally proposed to reverse the Eck fistula — *i.e.*, to ligate the vena cava, so that the entire blood-current passes through the liver — have never published such experiments; perhaps the result was fatal. But the arterio-venous anastomosis described above would appear to offer a means of studying the effects of long-continued arterial hyperemia of the liver, with no immediate impairment of well-being. From many points of view a research along these lines should promise some interesting results. The prompt recovery of the dogs, and their appearance of perfect well-being under such conditions, is remarkable.

2. Occlusion of the Portal Vein.

In Chapter XI was reviewed a portion of the literature regarding occlusion of the portal vein. Claude Bernard [(3), p. 316 ff, also p. 334 ff] devised the ingenious method of obliterating the portal vein by tying a stout ligature about it so as almost but not quite to close the lumen. The ends of this ligature were left protruding outside the abdomen. The ligature thus ulcerated its way out, and the slow complete occlusion of the vein was assured. According to Bernard, such animals show glycosuria not only on small doses of sugar, but also on a diet of potatoes. On the basis of his views concerning the hepatic function, this result seemed very easy to explain. But since that time, the Eck fistula has taken the place of Bernard's method, and has proved positively that the mere drainage of the portal blood into the systemic circulation is not a cause of glycosuria on starch diet. Yet the glycosuria observed by Bernard stands as a fact; he obtained it regularly, not in one but in many animals, and his word on such a question cannot be doubted. It therefore appears remarkable that this fact has attracted no further attention, and no one has attempted to explain it. One possible explanation is not far to seek, viz., that the portal stasis produced pancreatic injury, and that the condition of these dogs was a true *diabetes levis*. In particular, the rich blood-supply of the islands of Langerhans must at once occur to the mind, and the possibility that they are perhaps influenced in important manner by circulatory conditions.

Burdjenko in 1909 obliterated the portal vein by means of an aseptic method. A loop of silk was passed about the portal vein and secured to the Psoas or some other back-muscle. With the dog lying on his back, the loop made very little pressure upon the vein; but on standing up the vein was kinked and its circulation cut off. The dogs accommodated themselves to the conditions. Later, in second or third operations, the complete ligation of the vein was performed. Thirty-five dogs were operated upon in this manner, and were observed from 1 to 14 months. There seems to have been no record of glycosuria.

In Chapter XI, reference was made to the work of Gilbert and his pupils, who observed opsiuria and oliguria from partial ligatures of the portal vein. Gilbert and Chabrol observed chronic pancreatitis after this operation, but there is no record of glyco-

suria. Reference has also been made to the work of Natus, who studied carefully the chronic inflammatory changes in the pancreas produced by portal stasis.

Bolognesi ligated the portal vein in birds; but on account of the circulation of Jacobson, the result was only passive congestion of the portal area, with no particular anatomical changes.

Reference has previously been made to the evidences of pancreatic injury observed by Fischler in consequence of the Eck fistula.

Throughout this question, the possibility of nervous as well as circulatory effects must be considered; for we have seen that the piqûre may be of influence in connection with diabetes; and Thiroloix (6) claimed to modify the course of diabetes by operations upon the hepatic nerves.

On the clinical side, von Noorden [(3), p. 541] refers to Klippel and Lefas, Steinhaus, and Bleichröder, as having found that disturbances of the portal circulation may entail secondary changes in the pancreas. Ohlmacher suggested a connection between liver-disease, especially cirrhosis, and changes in the pancreas; but his evidence for an increase in the number of islets under such conditions was shown by Heiberg (6) to be insufficient.

Experimentally, it is evident that the method of Bernard is the one which has given the positive results, and accordingly it was the one adopted. The operation is very simple, but yet in practicing it and a number of slight modifications, there were five deaths and several failures from other causes. Woven ligatures have sometimes been gnawed off by the dogs. Wires have been tried instead, with the result of occasional death from kinking of the vein. For certain purposes it was desirable to use a large bundle of ligatures, and these in several instances gave entrance to infection, so that the animal died about a week later from abscess in the path of the drain. Enough was learned from these failures to permit the positive statement that neither an acute (fatal) stoppage of the portal vein, nor the prolonged presence of ligatures in that region, gives rise to glycosuria, either in normal or partially depancreatized animals.

Dog 104.

This is the only one of the failures in which the protocol is presented [Appendix]. On October 1, three-fourths of the pancreas was removed. October 19, a small wire was passed loosely

about the portal vein, with ends protruding. On November 20, the wire slipped out accidentally. It was thus in position for a month without causing any symptoms, though there was some question whether prolonged traction on the wire was not productive of polyuria. Subsequent operation proved that the portal vein was not obliterated. Sugar-feeding while the wire was in position showed that the tolerance was not lowered any more than is invariably the case in dogs that have lost three-fourths of the pancreas.

From these and similar animals it is concluded that the simple presence of a foreign body and its attending path of infection about the portal vein is not a cause of glycosuria, polyuria or other visible symptoms.

Here reference should be made to the records of Dog 73 and Dog 167, already mentioned in Chapter XI. These animals underwent exactly the same operation as the above, with the single exception that the loops surrounding the portal vein were much heavier. In Dog 73 there was no operation upon the pancreas; in Dog 167 most of the organ was removed. A condition resembling diabetes insipidus developed in both animals alike. It was shown in the case of Dog 167 that an animal in this condition is no more and no less susceptible to diabetes mellitus than a normal animal. In other words, simple obliteration of the portal vein seems neither to dispose to nor prevent diabetes.

But the true Bernard method is different from the above. It is not the passage about the vein of an untied ligature, which produces obliteration only after weeks; it is the sudden, nearly complete ligation of the vein, producing an immediate severe disturbance of circulation, with diarrhea and other symptoms as described by Bernard; and the complete stoppage of the vein and exulceration of the ligature occur within a few days.

Dog 166 (see protocol).

The remnant was more than one-fifth of the pancreas, and at autopsy it was found to have more than doubled in size. The true Bernard procedure was followed in this case, by tying the ligature about the portal vein as tightly as seemed safe; but probably even here the ligature was not quite as tight as Bernard tied it. The vomiting and diarrhea showed the results of portal stasis. In order to supply water, a large hypodermoclysis was given on December 15, and to strengthen the dog, 20 g. glucose

was added (less than 2 g. per kilo). I have shown previously that feeding or injection of sugar has no effect in producing diabetes.

The result was permanent diabetes gravis, a condition never obtainable under other conditions with a pancreas-remnant of the size stated. As usual, it was distinguished from a simple nervous glycosuria by the slow onset.

The microscopic findings in this and other animals are considered in the following chapter.

Remarks.

Here again conditions necessitated that a promising series be dropped. I believe however that the essential results were obtained. The interpretation which at present appears most probable is expressed in the following tentative conclusions.

1. The simple presence of an infected ligature surrounding the portal vein gives rise to no symptoms, either in normal dogs (several controls) or in a partially depancreatized dog (Dog 104).

2. The simple occlusion of the portal vein, when produced slowly enough, neither increases nor diminishes the tendency to diabetes (Dog 167). This deduction is in agreement with the results from the Eck fistula, and the negative findings (as respects glycosuria) of Burdjenko and of Gilbert and pupils, as contrasted with the positive observations of Bernard. It indicates that the mere failure of the pancreas (or its remnant) to drain into the portal system is not a factor in producing diabetes.

3. When a large mass of ligature (*e.g.*, a No. 3 picture wire) is passed about the portal vein without tying, the pressure upon the vein, perhaps by a circulatory change in the pancreas, gives rise to a condition of polyuria resembling diabetes insipidus, with retention of carbohydrate tolerance (Dog 73). The same condition develops in a partially depancreatized dog (Dog 167); and since such a dog can still eat bread without glycosuria, it is concluded that diabetes insipidus, if a disorder of the pancreas, is of different nature from diabetes mellitus, and is not necessarily accompanied by any lowering of carbohydrate tolerance. Exception may be taken to this suggestion, on the ground that the larger ligature produces greater nervous stimulation than a small ligature; that the polyuria is therefore not the result of pancreatic stasis, but is a reflex nervous phenomenon. This objection could be tested by using a small ligature and tying it

very lightly about the vein, so as to produce only slight stasis; this is an experiment which I have had to omit.

4. When the Bernard method is accurately imitated, by tying the ligature so as almost to occlude the portal vein, all the signs of portal stasis are greatly intensified, and the effect upon the pancreas is manifested by the production of diabetes gravis with a pancreas remnant which ordinarily is large enough to prevent even diabetes levis. The complete occlusion of the vein and the exulceration of the ligature are far more rapid in this way than when the ligature is left untied or loosely tied.

On this basis, the glycosuria observed by Bernard on starch diet receives a rational explanation. It seems also not unlikely that the same explanation may apply to the supposed "duodenal diabetes" reported by de Renzi and Reale. One clear case of glycosuria on carbohydrate diet was described by them, and has not been duplicated by them or by anybody else. It is recorded that the adhesions were very pronounced; and not improbably some kink or obstruction of the portal vein may have been produced somehow, with a result analogous to that of Bernard.

The most important outcome of the series of experiments is the indication that diabetes may result from a circulatory change in the pancreas. It must be borne in mind, however, that the circulatory change in this case is organic, and is followed by chronic inflammatory processes in the pancreas, as former authors have observed. It therefore corresponds to the type of human diabetes consequent upon arteriosclerosis or fibrosis. It does not correspond to the great majority of cases with little or no anatomical change in the pancreas, although it is conceivable that circulatory changes not accompanied by organic alterations may possibly give rise to diabetes.

A longer series of experiments of this sort is highly desirable, including different methods of ligature and other easily suggested variations. It should be applied to dogs both simultaneously with, before, and after partial pancreatectomy. It is obvious that the anatomical is as interesting as the physiological study. Comparative studies with the Eck fistula are also indicated, and may be expected to contribute evidence in two directions, both pointing against the specific rôle of the liver in diabetes; (1) the direct drainage of the pancreas through the liver is without specific importance, and the deflection of this drainage into the systemic vessels does not contribute to produce diabetes; (2) the

diminution of the blood-supply of the liver does not prevent diabetes, and there is doubt whether it modifies it at all. In this connection it is noteworthy that the diabetes in Dogs 166 and 167, with obliterated portal veins, ran the usual course in all respects. The same will presumably be found with the Eck fistula. It is true, as Minkowski (8) and others have emphasized, that the Eck fistula does not entirely exclude the liver. But, as authors already quoted have shown, it diminishes the blood-supply in such manner as to cause atrophic changes and great diminution of the glycogenic, biliary and presumably other functions. Furthermore, if Eck-fistula animals cannot survive the sudden ligation of the hepatic artery, it is probable that they can survive its slow obliteration by the Bernard or some similar method; and such a liver, being nourished only by the reflux flow of the hepatic veins and through insignificant adhesions, should be reduced to a maximum of atrophy and a minimum of function. Such animals should be interesting for various physiological studies, and in particular should contribute information to what extent the disordered processes of diabetes are carried on in the liver. It is a safe prediction that the Eck fistula, or any other method of reducing the hepatic function, will never cure diabetes. If the glycosuria shall be modified or even abolished, it will be only through a cachexia which masks the still unchanged diabetes.

The general conclusion is that the liver is without specific importance in relation to diabetes.

CHAPTER XXI.

ANATOMY.

THE structures especially requiring discussion here are the islands of Langerhans. The best review of the subject up to 1904 is given by Sauerbeck. A briefer account (in Italian) up to 1906–07 is that of van Rynberk. On the anatomical side, the complete review of the subject up to 1906 by Laguesse (10) is invaluable; a later and briefer summing up of his position is given by Laguesse (13). Opie (4) has interpreted the evidence up to 1910 strongly in favor of the islet theory of diabetes; while in the same year Lombroso (16) marshalled the known facts against this theory and in favor of the view that both islets and acini participate in the internal function. Lepine (6) also summed up the evidence in 1910. The most recent general review is by Gigon (2). The most recent and convincing anatomical study of the normal pancreas is by Bensley.

The literature concerning the islets will here be incompletely reviewed under the following headings.

1. History.
2. Comparative anatomy.
3. Histogenesis.
4. Descriptive anatomy.
5. Clinical pathology.
6. Experimental pathology.

1. History.

Langerhans (Dissertation, Berlin 1869), in the course of an admirable study of the pancreas, described the islets for the first time. Although not expressing a definite opinion, he suspected that they might stand in some relation with the nervous mechanism of the gland. Saviotti (ref. in texts) judged them to be merely the epithelium of ducts. Renaut named them "points folliculaires," and the term has been used to denote a lymphoid character of the structures, though Renaut did not mean it in

that way. Several authors upheld their lymphoid nature. Lewaschew considered the islets to be exhausted acini. Dogiel went farther and called them "dead points," because from the fat-droplets in the cells he supposed that they were degenerate portions of the parenchyma about to disappear by absorption. Harris and Gow, Gibbes, and Gianelli and Giacomini believed that the islets take part in the external functions of the pancreas, perhaps the elaboration of the diastatic ferment. There were indefinite suggestions in the early literature [see Sauerbeck] to the effect that the islets are embryonic remains, and more recently Karakascheff and Marchand have definitely stated the opinion that they are undifferentiated tissue from which new acini are produced. Gianelli and likewise Oppel [ref. by van Rynberk, and by Laguesse (10)] have looked upon the islets as atavistic structures, representing in higher vertebrates the tissue which in very low species (cyclostomes) constitutes the entire pancreas.

The credit of suggesting the islets as the organ of pancreatic internal secretion belongs to the anatomist Laguesse. Especially his embryological studies which showed that the islets are more numerous in the fœtus or new-born animal than in the adult, convinced him that they could not be exhausted acini. This fact, together with the rich blood-supply, the intimate relation of the cells to the blood-vessels, and the appearance and disappearance of granules interpreted as secretion, caused him in 1893 to hazard the opinion "that we are here in the presence of a manifestation of the internal secretion." This suggestion was ventured "sous toutes réserves"; but his more complete publication in 1896 expressed a more positive conviction, viz., "that the islands are the organ of the internal secretion, recently studied by the physiologists." Meanwhile Schaefer had announced to the British Medical Association in 1895 his belief in the internal secretory function of the islets, disturbance of which is the basis of diabetes. His statement attracted no attention in continental Europe, where interest was first aroused in 1899 by the expression of a similar opinion by Diamare, on the basis of comparative anatomical studies. The first clinical foundation for the insular hypothesis was then furnished, independently of each other, by Opie (1*A*, 2, 3) and by Ssobolew (2). Since then, the significance of the islets with respect to diabetes has been the principal question in the anatomy and pathology of the pancreas, and has dominated both the clinical and the experimental study.

2. Comparative Anatomy.

The islets were discovered by Langerhans in the rabbit (1869). Renaut in 1879 declared them to be constant in mammals and birds. Pugnat described them in birds in 1896. Kühne and Lea first demonstrated them in man in 1882. Harris and Gow in 1894 observed them in a long series of different animals; they missed the islets in snakes, and v. Hansemann in 1901 had also failed to find them in a python; but Pischinger in 1895 found them present in snakes and other reptiles, Giannelli and Giacomini in 1896 described them in still other reptilian species, and Laguesse has studied and pictured the reptilian islets very carefully. Von Ebner observed islets in the frog as early as 1872; Harris and Gow mentioned them as large but rare; Dewitt has found them numerous and small. The islets of the salamander, which Pischinger failed to find, were later studied in detail by Laguesse. One of the most complete works concerning amphibia was that of Richter in 1902; the latest is that of H. Fischer (1912). The islets in various fishes have been studied by Diamare, Pischinger, Rennie and Laguesse. One of the most interesting findings has been the constant presence in certain teleosts of isolated structures which are interpreted as consisting entirely of islet tissue; they have been dissected out and used for experiments in diabetic therapy by Rennie and Fraser. The exact status of the supposed islets found in cyclostomes is disputed. None have been discovered in amphioxus. Otherwise, their existence is recognized in all vertebrates. Their invariable presence in every individual of every vertebrate species has sometimes been called in question. Kasahara in 1896 doubted their constancy in man, and Dieckhoff missed them in a few autopsies. As late as 1910, Natus (2) could not see them in the living animal (rabbit), and in the prepared tissue occasionally found distinct islets absent. The practically universal opinion at present, however, is that notwithstanding wide normal variations in number and size, the absence of islets in any pancreas is eminently pathological.

3. Histogenesis.

Along with the early view of the lymphoid nature of the islets went also the opinion of authors that they were derived from the mesenchyme. As late as 1901 v. Hansemann believed them to be perithelial structures, from the blood-vessels.

Laguesse laid the first solid foundations of the embryology of the islets. He studied the pancreas of the sheep in a continuous series from embryos of 4 millimetres up to the adult type. Beginning as simple diverticula from the intestinal wall, the pancreas first consists of proliferating solid cords of cells. These become hollowed into tortuous anastomosing tubules, lined by a single layer of epithelial cells. According to Laguesse, the further development is as follows. Certain cells along the margin become differentiated to the extent of staining more deeply than the rest; these proliferate to form rounded masses of cells outside the tubules, which are the "primary islands." These later disappear, and are replaced by secondary islands, which likewise are transitory. In embryos of 60–65 millimetres the secreting acini are formed as buds from the primitive tubules, and consist of zymogen-bearing cells and centro-acinar cells. Islands of Langerhans are formed from the same tubules which form the acini, and the two kinds of structures are continuous. Islands merge into acini through cells of intermediate character, and each is readily transformed into the other. The same process is supposed to continue throughout life, although Laguesse later admitted that certain islands may become separated from their connections and retain the island form permanently. But the distinctive position of Laguesse is that islands and acini are interchangeable structures; that they merge and fuse one with the other; and that full-formed, secreting acini are transformed into islands, and islands likewise transformed into acini, in response to changing functional needs. This is the "balance" hypothesis of Laguesse, concerning the internal and external functions of the pancreas. It is still actively supported by the author and his pupils, and the same or similar views have been expressed by Lewaschew, Mankowski, Pischinger, Statkewitsch, Hansemann, Kollossow, Gentès, Perdrigeat and Triboudeau, Dale, Vincent and Thompson, Marrassini, Ohlmacher, De Meyer (7), Milne and Peters (1), and others. Karakascheff (and Marchand) claimed that acini may be formed from islets, and Herxheimer that islets may be formed from acini. H. Fischer, in a work just published, has studied the islets in the frog, toad, triton, bat and guinea-pig, and has reported numerous and unmistakable transitions between islets and acini.

On the other hand, Massari and also Diamare took the position that the islets are independent and unchanging structures, formed

in embryonic life and thereafter as constant and unalterable as the renal glomeruli. The views of numerous other opponents of Laguesse will require notice later.

The first study of the embryology of the islets in man was that of Renaut (ref. by Pearce), who observed them in a human embryo of the third month, and confirmed the description given by Laguesse for the sheep. Pearce (1) in 1902 made a more complete study, on the basis of 21 human embryos of different ages. He found that the islets develop by proliferation and differentiation of the cells of the pancreatic tubules, and lie as small round or oval masses in direct cellular continuity with the acini. Later (at about the third month) the connecting stalk becomes constricted by connective tissue, and finally complete separation takes place, along with vascularization and reticulum-formation in the islets, increase in the number of cells, and their arrangement in cords. The growing acini surround these islets, which thus come to occupy the interior of the lobules. In syphilitic pancreatitis of the new-born, the earlier embryonic conditions are still visible, owing to the arrest of development. The author maintained the complete differentiation and permanent independence of the islets of Langerhans.

Karakascheff (1 and 2), studying luetic fœtuses, described the development of the islands from proliferating buds of the ducts. The islets enlarge by multiplication of cells, and from the cells of the periphery tubules are formed; the cells composing these acquire zymogen-granules, and thus typical acini arise from the islets. Because of this formation of acini from the peripheral portions of islets, the latter come to occupy the centres of the lobules. The process is supposed to continue in post-embryonic life, and the islets represent undifferentiated tissue from which on occasion new acini are produced.

Küster (1904) found that the islets in early embryonic life originate as buds from the ducts, but later there is complete separation. The fully formed islets lie close against the acini, often without intervening capsule, but transitions never occur. Post-embryonic growth of the pancreas is solely by increase in size of the existing islets and acini, not by formation of new.

Helly in 1906 claimed to distinguish (in the guinea-pig) certain cells, destined to form islets, at a stage when the pancreas-anlage still consists only of solid cell-masses. He also described two types of islets in selachians. He concludes that all vertebrates have

islets, which are organs *sui generis*, and at no stage of development, early or late, is there any sort of transition between islets and acini.

Weichselbaum and Kyrle in 1909 studied a number of human, dog, and guinea-pig pancreases at various stages of embryonic and post-embryonic life. In essentials they confirmed Pearce and Küster; the islets develop from the ducts, and there are no transitions between islets and acini. In regenerative processes in the adult gland there may be an active development of islets; and even normally they probably to some extent disappear and are replaced. Although both acini and islets arise from the ducts, yet mitoses are found under certain conditions in both, and therefore both can to some extent regenerate themselves.

The most recent embryological study is that of Mironescu, who comes to the following three conclusions; (1) The first anlage of the islands of Langerhans is formed by the vascularization of epithelial buds, which arise from the ducts and acini; (2) the islands are recognizable only by the arrangement of their cells and their relations to the blood-capillaries; (3) the formation of new islands after birth probably proceeds by the same process as before birth. The author believes in a formation of islets from acini, but has never observed formation of acini from islets.

The question of transitions will recur repeatedly in the ensuing topics. Opie has steadily opposed the idea of mutual transformations between islets and acini. He suggests [(4), p. 73] that some authors have described as islands of Langerhans, acini in which centro-acinar cells are unusually numerous. He also has observed confusing pictures in the human pancreas, suggesting transitional types: "The cell-protoplasm does not take the nuclear dye as does the basal part of the ordinary glandular cell, and when stained with eosin has a bright pink color and homogeneous refractive appearance. The nucleus, which shows no evidence of degenerative change, is situated near the centre of the cell. Occasionally one or more cells of the character described form part of an acinus which otherwise resembles those about it. Usually, however, a group of acini are changed, and such an area may roughly correspond in size to an island of Langerhans." Opie regularly finds, however, that on careful search the presence of a lumen and the relations revealed by serial sections serve to demonstrate the acinar nature of these formations. Dewitt also admits the occurrence of appearances which resemble transitions, but by serial sections and wax models she formed the conclusion that the islets and acini

are contiguous, not continuous. Numerous others to be mentioned have strongly opposed the idea of transformations between full-formed islet and acinar cells. Bensley's recent work is strongly against such a process.

In general, it is fair to state that the question is not yet fully decided, but that the balance of evidence is beginning to favor a view intermediate between the two extremes. The one view, that the islets in post-embryonic life are as constant and unchangeable as the renal glomeruli, may safely be discarded. Laguesse's opposite extreme, that mutual transitions and transformations between islets and acini are a common and normal process, is also becoming improbable. Whether under abnormal conditions such transformations may ever occur is not yet decided. The best evidence indicates that both acini and islets may be formed from the ducts at any stage of existence, but that normally the cell of one type is not transformed into the cell of the other type.

4. Descriptive Anatomy.

The description of the islets may be presented in the following divisions:

A. Number and size.
B. Location and form.
C. Capsule and reticulum.
D. Vessels and nerves.
E. Relations to ducts.
F. Cytology.

A. Number and Size.

In both of these particulars the islets vary widely. The largest known forms are the isolated islets of certain teleosts, which according to Rennie may measure 5×14 millimetres. Species which possess large and numerous islets are man, rodents (notably guinea-pigs and rats), birds (some islets large, others small), and a few others. In guinea-pigs, pigeons, etc., they are said to be visible with the naked eye. In snakes they may measure 2 or 3 mm. In man they are classified by Laguesse as ranging from less than 100 μ to more than 400 μ in their greatest dimension; Ssobolew has spoken of them as attaining even 1 millimetre. Small islets are supposed to be characteristic of dog, cat, and most amphibians. They are of medium development in cattle and sheep.

Laws have been suggested, for example by Ssobolew and by Gentes, that islets are abundant in small animals with active metabolism, and by Frugoni and Stradiotti, that species with high carbohydrate tolerance are rich in islets. No rule holds; we know of no constant relation to the activity of metabolism, carbohydrate tolerance, diet, habits, or position in the animal scale. It is true that they reach a high development in some of the higher species, especially in man, and this fact has been well used by Laguesse to combat the idea that they are vestigial structures.

The comparative number and size of the islets in different individuals of the same species becomes a matter of importance, since some pathologists undertake to base upon it a microscopic diagnosis of diabetes. Many of the older statements concerning this point are unreliable, because based on examination of only a few sections. Counts, measurements, and calculations of the size and bulk of islet tissue have been made by Opie, Sauerbeck, Laguesse, Dewitt, Heiberg, Cecil (4), and Bensley. Four points may be noted. (1) Authors are agreed that islets vary in number in the different portions of the pancreas, and are most numerous in the splenic end. Opie's average furnishes a comparison as follows; head 18.3, body 18, tail 34 (= number of islets in sections of 0.5 square centimetre, 10 μ thick). Gianelli [ref. by Laguesse (10), p. 44] formed the opinion that only the dorsal pancreas can produce islets. In transplantation experiments, Kyrle found that tissue from the duodenal end tends to produce acini, while that from the splenic end produces more islets. But Laguesse (l.c.) refutes the idea of a strict limitation of islet-forming power to the dorsal pancreas. (2) Normal individuals vary widely in the number and size of islets. Heiberg estimated the actual weight of islet tissue in a human pancreas which he examined as 2.6 g. In three human glands, Dewitt estimated the islet-tissue at $\frac{1}{250}$, $\frac{1}{500}$, and $\frac{1}{5000}$, respectively of the total weight of the organ. The wide individual variations between guinea-pigs are shown in tabular form by Bensley. Cecil (4), using dogs, found the usual wide normal variations; but on the average the ratio of islet-tissue to the pancreas was 1.2:100, i.e., a trifle over 1 per cent. (3) Islets are relatively more numerous in very young individuals. On the basis of this relative abundance, it has long been disputed whether the infantile pancreas contains the full number of islets represented in the adult gland, or whether the number of islets increases during the growth of the organ. Bensley epitomizes his

findings with guinea-pigs as follows: "In the whole series there were only three animals in which the number of islets was greater than in a guinea-pig two days old and weighing 74 g. There are however certain facts which indicate that during the first two weeks of life there is a reduction in the actual number of islets, and that thereafter there is a slow production of new islets." (4) Bensley's examination of the islets has been by means of a method of vital staining, which throws them into sharp relief. The important bearing of his work upon all previous investigations is evident from the following. The size of the (guinea-pig) islets varies from 0.5 mm. down to single cells. The total number of islets revealed by the vital staining method is approximately 20 times as great as the number found by Dewitt by simple counting in sections. The islet content of adjacent portions of the same pancreas may vary within wide limits, so that estimates of the total number based upon samples from several different parts may give entirely misleading results.

In view, therefore, of the wide normal variations, the fact that total counts of the entire pancreas have not been the rule, the possibility of large errors even under favorable conditions, and the immensely increased chances of error in pathological tissue, it becomes very doubtful how much importance can be attached to existing statements concerning alterations in the size and number of islets in connection with diabetes.

B. Location and Form.

The great majority of the islets are situated in the interior of pancreatic lobules. By Opie and Flint, a particularly regular arrangement has been observed in the cat's pancreas, where almost every lobule has an islet near its centre. The customary position of the islets has been used as an argument against the hypothesis of transitions, according to which one should expect that, by transformation of acinar tissue, islets should occur equally in all localities. Laguesse acknowledges a "simple predilection" for the centre of the lobules. Islets also occur in the interstitial tissue of the pancreas, and along the ducts, free from all connection with acinar tissue; this was shown by Dewitt for the guinea-pig, and confirmed by Bensley for the guinea-pig, dog, cat, rat, and rabbit.

With minor differences, the general form of the islets remains the same throughout all species. The wax models of Dewitt give the best idea of their appearance. They may be thought of as

esembling a sponge with exaggerated pores, the sponge tissue hen representing the anastomosing cords of cells which compose he islet, and the pores representing the spaces occupied by the lood-vessels. The typical form is irregularly spheroidal, and his description applies to man; but they may be elongated, ranched, or lobed; or according to Bensley may consist of merely one or a few cells distributed with the other cells of an cinus or small duct.

C. Capsule and Reticulum.

Considerable discussion has taken place concerning the exis- ence of a capsule, because of its bearing on Laguesse's transition ypothesis. Most of the earlier authors, including Laguesse, lenied the existence of any distinct capsule. Gentes claimed to ind a limiting membrane and peri-insular cleft, which we may nterpret as artifacts. Opie has found indications of an incomplete apsule. Flint, using the Spalteholz digestion method, demon- trated that the typical islet of the cat possesses a distinct capsule nd reticular framework strikingly different from that of the urrounding parenchyma. Attention has been called to the solated and encapsulated islets of some fishes. On the other and, in amphibia and other low forms, authors from Diamare o Fischer have found strict contiguity of islets and acini. Dewitt ailed to demonstrate a capsule, and looked upon fibrous bounda- ies as secondary if present. Bensley has explained the dis- greement, by finding several different classes of islets, especially me which are primary in the lobules and directly contiguous ith the acinar cells, and others which have become secondarily cluded in the lobule and hence are marked off from it by a little brous tissue.

The framework of the islet consists of a delicate reticulum ccompanying the vessels. The latter are not surrounded by a brous coat, but the epithelial cells of the islet rest directly upon e endothelial cells of the capillaries. This arrangement has been terpreted in favor of the internal secretion theory.

D. Vessels and Nerves.

The very rich blood-supply of the islets is one of their striking atures. The glomerular network of capillaries was demon- rated by Kühne and Lea in 1876. Authors are agreed that

there is no one hilum or pedicle for an islet, but that the vessels may enter from any direction. There is still some question concerning the angiology. The majority of investigators have considered the islets to be supplied either by capillaries alone, or by capillaries and arterioles. A smaller number have considered the blood-supply to be venous, and Dewitt in particular has described capillaries and sinusoids in the islets, and afferent and efferent veins. Details may be found in the paper by Dewitt, and in the general review by Laguesse (10).

The richness of the nervous as well as the vascular supply distinguishes the islets from the acini. The nerve-supply was described in Chapter XVII.

E. Relations to Ducts.

This again has been a disputed point in connection with Laguesse's doctrine. Injections of the pancreatic ducts by v. Ebner and Kühne-Lea failed to show a lumen in the islets; while Lewaschew claimed to succeed in injecting the islets from the ducts, and Mankowski, with silver nitrate injections, made a similar claim. Laguesse in particular has described intimate relations between the islets and the ducts, and, especially in lower species, has asserted the existence of delicate lumina in numerous islets. A close connection with the ducts has been found by Helly in selachians and by Fischer in amphibia. Dewitt demonstrated no lumina in the islets. As previously noted, many of those who have studied the development of the islets have asserted that they finally become completely independent of the ducts. The conflicting views may be explained by Bensley's work. He recognizes a few exceptional islets which have lost all connection with either ducts or acini. Most striking however is his demonstration of an elaborate and intricate system of tubules and cell-cords forming a web about the ducts in many places, and connecting them with the islets and sometimes with acini. The cells of these tubules are small, polygonal, of a low order of differentiation, and apparently able to give rise to either islets, acini, or mucous glands. Through this system of tubules the great majority of the islets stand in permanent relation with the ducts. The islet itself, however, has no lumen, but is merely a ball of cells; in the rare instances where the lumen is prolonged a little way into the islet, the cells of this portion are generally duct-cells rather than islet-cells.

F. Cytology.

The simplest arrangement is typified in amphibia, where frequently cylindrical cells are placed side by side in single rows, with both ends in contact with the capillaries. In most other species however the cells are small, irregularly polygonal, and packed together in cords and masses; they are most abundant at the periphery of the islet, which is least vascular, and the cords generally become thinner toward the centre of the islet, where the vessels are largest. Cell boundaries are sometimes hard to make out, and the structure was formerly supposed to be often a syncytium; but Bensley has shown that the individual cells can always be separated by appropriate means.

Perhaps the most puzzling problem in the anatomy of the pancreas has been to distinguish strictly between islet cells and acinar cells. Many erroneous conclusions have probably arisen from the tendency to classify any small cell, not in a duct and not containing zymogen granules, as an islet cell. Thus resting or exhausted or otherwise altered acinar tissue has been mistaken for islets. Opie has called attention to the bright pink of the islets in eosin-hæmatoxylin preparations, in contrast to the deeper basophilic stain of the acini. Sauerbeck has laid emphasis upon the occurrence of occasional giant nuclei in the islets. Diamare and Sauerbeck regard as normal a gnawed-out (angefressen) or half-dissolved appearance of the cells, which Weichselbaum and Stangl consider pathognomonic of diabetes. Most of the earlier authors described the cytoplasm as clear, but others observed granules, much smaller than zymogen granules. Laguesse [(10) and elsewhere] has described the cell-structure in detail. He gives the dimensions in man as varying from 5 μ to 20 μ, but approves v. Ebner's statement that the average diameter is 9–12 μ. The nucleus is said to be situated toward the side farthest from the capillary; it is spherical or ovoid, large compared to the size of the cell (about 5 μ), with an occasional giant form (about 10 μ). The nuclear membrane is thin, the chromatin granules large and abundant, and the large eosinophilic nucleolus characteristic of the acinar cells is lacking. After fixation in Müller's fluid the cytoplasm is clear; by other methods granules and vacuoles of secretion appear. The granules may be pressed out from the fresh cell and observed free. The abundant fat-droplets of the cells caused Dogiel to regard the islets as "dead points," but the fat is according to Laguesse not constant.

Diamare, Schulze, and Dewitt recognized two types of islet cells. By Lane in 1907 they were distinguished as "A cells" which contain granules preserved by alcohol, and "B cells" which contain granules preserved by chrome-sublimate solution. Both sorts of granules are dissolved by fluids containing acetic acid. Various chemical distinctions were found between the granules. The neutral gentian stain was recommended for differentiating the islet cells from the acinar cells. This latter claim was confirmed by Mary B. Kirkbride in 1912, who however failed to distinguish two different types of cells. Bensley has carried the differentiation to its highest point. Besides the A and B cells he also finds islet-cells free from granules, and he concludes that the A and B cells are not transitions or different functional states of the same cell, but are independent and are each developed from an undifferentiated duct-cell. He also distinguishes the three principal elements of the pancreatic parenchyma on the basis of cytological characteristics; viz., for the acinar cell, zymogen and prozymogen granules, basophile substance, mitochondria, etc.; for the islet cell the typical fine granules; for the duct-cells and centro-acinar cells mitochondria, fuchsinophile bodies, and nucleus relatively poor in chromatin. On this basis he distinguishes the individual cells even when situated amid those of another type, and denies that anything resembling mutual transformations of islet and acinar cells is seen in the normal pancreas, though admitting the unproved possibility that under some conditions such transformations may occur.

5. Clinical Pathology.

The subject may be considered in the following divisions:

A. Miscellaneous lesions.

B. Lesions in relation with diabetes.

A. Miscellaneous Lesions.

Those of interest here are:

I. Necrosis.

II. Degeneration.

III. Tumor.

I. *Necrosis.* — Besides the detailed description by Opie (4), reference may be made to the paper of Coenen and the dissertation of Riegg. The latter reported a case in which the urine was free

from both albumin and sugar. The fact that in pancreatic necrosis apparently the entire organ may be destroyed and yet the patient not show diabetes, is ordinarily accounted for by the rapid course and intense prostration. That glycosuria does sometimes accompany this condition is illustrated in cases mentioned by Garrod (2).

II. *Degeneration.* — The occurrence of fat in normal islet cells has previously been mentioned. Stangl found that the droplets appear late in embryonic life, and increase up to old age; he therefore considered them a product of normal activity. Weichselbaum and Stangl (1) laid emphasis upon the increased fat-content of the islets in numerous diabetic patients, and regarded it as a fatty degeneration, of etiologic and diagnostic importance. Symmers looked upon the presence of fat as pathologic; he finds it more frequently associated with alcoholism than anything else, and not pathognomonic of diabetes, for the islets of diabetics may be devoid of fat.

Amyloid degeneration may involve the islet vessels. Hyalin degeneration has been described by Opie especially in connection with diabetes.

III. *Tumor.* — Nichols in 1902, Helmholz (1) in 1907, Cecil (2) in 1911, and Alezais and Peyron in 1911, reported tumors of the pancreas apparently composed of islet tissue. The last-mentioned case is doubtful, for the neoplasm apparently arose from the acini, and might therefore conceivably consist of altered acinar cells. The existence of islet tumors has been interpreted somewhat in favor of the independence of islet and acinar tissue.

B. Lesions in Relation with Diabetes.

The early observations of Bouchardat, Lancereaux and others who first directed attention to the pancreas need not be reviewed here. Interest has shifted from gross to microscopic studies, and these may be considered in subdivisions according to the three hypotheses which now hold the field:

I. The acinar hypothesis.
II. The acino-insular hypothesis.
III. The insular hypothesis.

I. The Acinar Hypothesis.

Hansemann in 1894 claimed to have discovered a specific type of pancreatic atrophy in a number of cases of human diabetes.

He named it "granular atrophy," in comparison with granular atrophy of the kidney. The observation closely resembled that of Opie, for Hansemann has admitted that the change is essentially equivalent to Opie's interacinar fibrosis. He however laid emphasis upon the acinar tissue as the basis of the disease. His later publications (2 and 3) uphold the same opinion; and also in 1909, in his discussion of the paper of Herxheimer (2), he has maintained that the islets are not constant and not independent; they form and are formed from acini; their number varies greatly at different times, and they have nothing to do with diabetes. In some of his reported cases, he found no organic change in the pancreas or elsewhere in the body, and was forced to assume a functional diabetes. In other cases he found the pancreas apparently replaced entirely by cancer-tissue, without diabetes, and here he set up the hypothesis that the tumor cells take on the function of the gland-cells.

Gutmann reported 3 diabetic autopsies, and concluded from them that diabetes may exist without changes in the islets.

Schmidt reported 23 diabetic autopsies, in 8 of which the pancreas was entirely unchanged, while in 15 there were changes present. In two cases the islets alone were affected, in one by hyalin degeneration, in the other by interstitial inflammation. In four other cases the islets were chiefly involved. In two further cases islets were numerous and large, and in the author's opinion these islet-nests resulted from transformation of acini.

In general, the pure acinar hypothesis has very little support at the present time.

II. The Acino–insular Hypothesis.

This is the youngest of the three hypotheses, and was first suggested by Reitmann in 1905. The essential idea is that both islets and acini participate in the internal function of the pancreas; and that this function, normally performed by both, can in necessity be performed by either alone. Reitmann's own report included 17 cases of diabetes; also studies of some developmental anomalies and the fresh glands of executed criminals. He considered that the islets are without etiologic importance. The most significant process in his opinion is a fibrosis resembling Hansemann's "granular atrophy." It is in the nature of a chronic destructive process with partial regeneration, as in cirrhosis of the liver. Such changes are viewed as an exaggeration of the degen-

erative and regenerative processes occurring in the normal pancreas, and they may lead to a complete reconstruction of the gland.

Herxheimer (1) reported 5 diabetic autopsies summarized as follows. (1) Transitions were found always present, and were always interpreted as formation of islets from acini; never the reverse. The process is presumably regenerative. (2) The acinar tissue regularly showed partial disappearance and replacement by fibrous tissue. (3) Adenomatous proliferations as large as 4 mm. diameter were observed in 3 cases, arising sometimes from the ducts, sometimes from the acini or islets. The author suggests the name of "pancreatic cirrhosis." His opinion is that the islets have no specific importance. The internal secretion of the gland is furnished by both the islet and acinar tissue; if the latter is diseased, the islets alone are able to perform the internal function.

Karakascheff (1 and 2), working under Marchand, reported 16 diabetic autopsies and a number of studies of embryonic glands. He regularly found transformation of islets into acini. Diabetes may occur when the islets are normal or even hypertrophied, while other cases with considerable destruction of islets show no diabetes. The islets are reserve-tissue; they serve only to replace worn-out acini; they are not a separate organ and do not constitute the basis of diabetes. Hypertrophy of the islets occurs in diabetes only as an effort to regenerate acini. The whole parenchyma is in relation to diabetes, not merely a part.

Lombroso has not subscribed to the doctrine of transitions between islets and acini, but has become the most active supporter of the view that diabetes depends upon a disorder of the pancreas as a whole. His entire review of the question (16) is an argument in favor of this hypothesis, which is one that must be seriously reckoned with. Lepine [(1), p. 179] has declared in favor of this view.

III. The Insular Hypothesis.

In 1900 and 1901, Opie (1*A*, 2, 3) published observations concerning chronic pancreatitis, with and without diabetes. He established the distinction between two types, as follows: (1) interlobular pancreatitis, in which the inflammatory process is localized chiefly at the periphery of the lobule and involves the islets only after it has reached an extreme grade; (2) interacinar pancreatitis, in which the process is diffuse, invading the lobules, separating individual acini, and involving the islets. A relationship was

pointed out between diabetes and disease of the islets, inasmuch as diabetes was found absent when the pancreas was extensively diseased but the islets little affected, and present in cases of inflammatory or hyalin change of the islets with little involvement of the remaining parenchyma.

Ssobolew (2) in 1901 and 1902 reported a series of 21 non-diabetic and 15 diabetic autopsies. The diabetic changes described were atrophy or sclerosis of the parenchyma, and especially alterations in the islets; qualitative changes were limited to 3 instances of atrophy or degeneration, but quantitative changes were more marked, viz., 4 cases of complete absence of islets, 9 cases of diminution of number, and 2 cases with no visible change in the islets.

Wright and Joslin found islet changes in 2 out of 5 diabetic autopsies. One of these in particular was a hyalin degeneration of the islets with practically no change in the rest of the gland.

Herzog published 5 cases. In one, islets were completely absent and replaced by scar-tissue; in another they showed hyalin degeneration; in the other cases they were also changed.

In 1904 Sauerbeck published his notable review of this subject, including all the known literature up to that time, with observations of his own, and with a masterly analysis and critique. He declared in favor of the insular hypothesis. In the same year appeared studies by Sauerbeck, Ssobolew, Gutmann and Adler, occupying a supplementary volume of Virchow's Archiv.

Hoppe-Seyler (2) published cases showing the relation of arteriosclerosis to pancreatic lesions, and concluded that involvement of the islets is the essential factor in diabetes. Bleibtreu's observations are somewhat similar, with the suggestion of an underlying nervous cause. More recently, Saltykow has reported nine autopsies, in one of which arteriosclerosis was associated with pancreatic atrophy, fibrosis of islets, and diabetes.

Thoinot and Delamare examined the pancreas of seven diabetics. The findings were not uniform, but there were some selective islet changes. The general views of the authors favor the insular hypothesis. No changes were found in the adrenals, thyroid or hypophysis.

Gentes and Fischer each found sclerosis of the islets in single autopsies. Curtis and Gelle described transition forms in the sense of Laguesse in connection with diabetes, and attributed diagnostic importance to them. Gelle considered the acino-islet

changes important in preventing diabetes in pancreatic cancer. MacCallum (1) observed hypertrophy of the islets in a case of diabetes. Halasz (2) in some diabetics has found islet-changes, in others none; he suggested that carbohydrate metabolism is under the control not of one gland but of many, and some cases of diabetes, especially the milder sort, may not be of pancreatic origin. Diamare (2) and Visentini (1*A*) have presented clinical evidence for the islet hypothesis.

Reports of conditions in which the pancreas has been extensively changed, but without destruction of islets and without diabetes, are too numerous to review in detail. For example, Pearce (2) found that in cancer the islets are generally preserved, and may show an appearance of compensatory hypertrophy. Halasz (1) found the islets well preserved in many areas in sarcoma of the pancreas, even though the whole gland seemed to be replaced by tumor. Ohlmacher described several cases of combined hepatic and pancreatic disease, with what seemed to be compensatory hypertrophy of the islets. [Heiberg (6) considered increase of islets improbable in these cases.] Keuthe reported a case of advanced atrophy of the pancreas without diabetes; only a trifle of acinar tissue remained, but numerous large islets were present, scattered throughout the connective tissue.

One of the most interesting of all cases in this category was reported by Scott. "There was a hard carcinomatous growth at the head of the pancreas, which was shown, by careful dissection and vain attempts to pass a bristle from behind, to obliterate completely the ducts of Wirsung and Santorini. The gland behind the growth was a little narrower than usual, but, apart from great dilatation of the duct, there was nothing striking to be seen on examining the cross section. . . . Microscopically, the pancreas consists of an external coat of adipose tissue, with a central core of connective tissue, containing islands of Langerhans, nerves, blood-vessels, and a few ducts. No acinar tissue has been seen in any section. . . . The islands of Langerhans, on the other hand, look perfectly normal. . . . The connective tissue is composed of delicate fibres, and cuts easily. . . . A large part of the fibrosis in this case I am inclined to regard as apparent rather than real — in other words, much of the connective tissue present is the original connective tissue of the gland fallen together during the atrophy of the acinar tissue. The marked tortuosity of the vessels speaks in favor of this view. . . . No glycosuria was ob-

served during life. This is what would be expected on the island theory of diabetes."

Three long and important series in support of the insular hypothesis remain to be considered, viz., those of Heiberg, Cecil, and Weichselbaum and Stangl.

Heiberg has emphasized the functional and anatomical independence of the islets, and the importance of quantitative changes. He states (4) that even in diabetic cases which show apparently no changes in the islets, there is a marked reduction in their number, *e.g.*, 30 or 40 per field as against 130 normal. The disappearance is attributed to degenerative and inflammatory processes. He (7) has also reported two autopsies in young diabetic children, and (10) one case of atrophy and lipomatosis with diabetes insipidus and mellitus. Heiberg (5 and 8) explains the rarity of glycosuria with pancreatic cancer as due to preservation of the islets; when diabetes exists with cancer, there are indications that in some cases at least it preceded or developed independently of the cancer. Heiberg (9) lays stress on both quantitative and qualitative changes; he asserts that pancreatic changes can be demonstrated in every case of diabetes, and in certain cases the changes are so strictly limited to the islets as to prove that these are the anti-diabetic elements of the pancreas.

Cecil (1) reported a series of ninety diabetic autopsies. Among a dozen interesting conclusions, the following may be quoted. "Anatomical lesions of the pancreas occur in more than seven-eighths of all cases of diabetes mellitus. In diabetes associated with lesions of the pancreas, the islands of Langerhans constantly show pathological changes (sclerosis, hyalin degeneration, infiltration with leukocytes, and hypertrophy). In some cases of pancreatic diabetes (12 of 90 cases) the lesion of the pancreas is limited to the islands of Langerhans. . . . Diabetes mellitus occurring in association with hæmochromatosis (bronzed diabetes) is referable to pigmentation and destruction of the islands of Langerhans." Cecil (3) studied especially hypertrophy and regeneration of the islets. One or the other condition was present in 34 out of 100 diabetic autopsies. Hypertrophy may be either an increase in size of existing islets, or a formation of new islets from the ducts. Analogous processes were also found in a majority of 33 cases of chronic non-diabetic pancreatitis. They were present in 1 of 17 cases of pancreatic cancer, and in several other cases in which the pancreas was almost normal.

Weichselbaum and Stangl, and more recently Weichselbaum, have reported the largest series in the literature. Weichselbaum (3) claims to have found unmistakable changes of the islets in every one of his 183 cases. The alterations described are qualitative; they consist in atrophy, sclerosis, hemorrhage, and hyalin, fatty and "hydropic" degeneration. The last condition is one of vacuolization and dissolution of cytoplasm, leaving a naked nucleus. Regenerative processes also occur; the islet cells multiply, and there is formation of islets from ducts. Transitions between islets and acini are never seen. The findings are interpreted strongly in favor of the insular hypothesis.

From the above incomplete survey of the literature, it is evident that the insular is the dominant hypothesis; its opponents will probably admit the fact. As methods of study have improved, the finding of unquestionable pancreatic changes in diabetes has increased. A well-marked subjective element is still present; the findings of different observers are considerably different. High proportions of pathognomonic lesions are reported by some writers; but if any pathologist were required to take the autopsy material of a hospital, without information, and pick out the cases of diabetes, it would be safe to predict a considerable percentage of error. Every anatomical hypothesis of diabetes still requires to be assisted by assuming the existence of a certain proportion of functional cases without known anatomical basis.

6. Experimental Pathology.

This subject may be considered in the following divisions:

A. Attempted modifications of pancreas through its internal function.

B. Attempted modifications of pancreas through its external function.

C. Miscellaneous experiments.

D. Isolation of pancreatic tissue.

A. Attempted Modifications of Pancreas Through its Internal Function.

The earliest attempts to produce anatomical changes through functional influences upon the pancreas were by means of fasting, food, and sugar. The experiments and interpretations were

sometimes from the standpoint of the internal, sometimes from the standpoint of the external function, and for convenience they will be considered together under the latter heading.

As stated in Chapter XV, phloridzin, and, as stated in Chapter XVI, adrenalin, have been used in the attempt to produce effects upon the pancreas, but both of them are without specific influence upon either the structure or the function of this gland.

As mentioned in Chapter XII, the attempts of Ssobolew, Klimenko, De Meyer, and Rinderspacher to produce changes in the islets by means of specific cytotoxic sera have yielded negative results.

J. Lepine injected guinea-pigs with "diabetogenous leukomaines" prepared by the method of R. Lepine and Boulud, without significant results.

Carnot and Amet subjected animals to chronic poisoning with arsenic, phosphorus and morphin. In the severe cases they claimed to find frequently a fatty degeneration, and in cases of slighter poisoning a hyperplasia, of the islands of Langerhans. They looked upon the islands as probably the most vulnerable part of the pancreas. Heiberg (6) disproved their claims regarding hyperplasia of the islands.

B. Attempted Modifications of Pancreas Through its External Function.

The favorite methods have been with:

I. Pilocarpin.
II. Secretin.
III. Food and fasting.

I. Pilocarpin.

One of the proofs claimed by Lewaschew for his view that the islets are merely exhausted acini, was that pilocarpin, by forcing the gland to intense secretion, greatly increases the number of islets. Several successive doses of pilocarpin were said to be necessary for the greatest increase in number. Massari obtained entirely negative results from pilocarpin in eels. Mouret (5) performed pilocarpin experiments in dogs and frogs, and says nothing of islet changes. Mankowski by laparotomy removed specimens of the pancreas of dogs before and after doses of pilocarpin, and supported Lewaschew's statement. Ssobolew (2)

also used the laparotomy method, and found no change in the islets from pilocarpin. Hansemann obtained entirely negative results with both pilocarpin and atropin. Opie (1), by treatment of a dog with pilocarpin once daily for 9 days, or 6 or 7 times during the same day, found no change in the number of islets. The question of pilocarpin is thus decided in the negative.

II. Secretin.

Dale found transition-forms normally present in the cat, dog, rabbit and toad. By intravenous injections of secretin, prolonged for several hours, in cats and dogs, he claimed to find a new-formation of many large irregular islets at expense of the acini; some of the new islets still showed alveolar arrangement, and transitional types were numerous. In dogs, almost an entire lobule might be thus transformed. Toads responded to secretin by a transformation of the greater part of the pancreas into islet tissue.

Vincent and Thompson (1 and 2), after describing the normal histology of the islets in a series of mammals, birds, reptiles, amphibians and fishes, supported the claim of Dale that secretin markedly increases the number of islets.

The above conclusions are probably an example of errors arising from confusion of exhausted acinar cells and islet cells, or from postmortem changes. Bensley has proved conclusively that secretin does not increase the number of islets in either the guinea-pig or the toad, and Cecil (4) has obtained convincing negative results in dogs.

III. Food and Fasting.

Experiments with starvation, protein feeding, carbohydrate feeding, glucose feeding, glucose injections, and combinations of these are so inseparably connected that they will be considered here together, though often, especially with glucose, the attempt of the investigators has been to stimulate the internal secretion of the pancreas. Two groups may be considered; (*a*) Authors announcing positive results; (*b*) authors announcing negative results.

(*a*) *Authors Announcing Positive Results.*

Lewaschew, who originated the doctrine that the islets are exhausted acini and believed that he could inject them from the ducts, performed not only the first experiments with pilocarpin

but also with food and fasting. Withdrawal of food and water, by resting the pancreas, diminished the number of islets. A heavy meal, by stimulating secretion, increased the number of islets. These findings are opposite to those of the other authors who have announced positive results.

Statkewitsch, studying the pancreas in advanced starvation, observed that the cells of many acini shrink, become clear, and form "little heaps," which he thought probably identical with islets.

Mankowski carried out an investigation on an extensive scale, but his method, of subjecting dogs to successive experiments followed by successive laparotomies to obtain pancreatic tissue, necessarily involved error. He tried the effects of starvation, electric stimulation, and of introducing into the alimentray tract carbohydrate, fat, albumin, alkali, acid, etc. He found numerous transition forms corresponding to the various functional conditions. Fasting produced a transformation of acini into islets. Intravenous injection of dextrose produced no increase.

Dale found an increase in both the number and size of the islets in starvation, though the results were less marked than from secretin. On the other hand Vincent and Thompson found fasting more effective than secretin; the islets of fasting animals were increased both in number and size, especially in the splenic portion; and areas of acinar tissue incompletely transformed into islets were also seen. The conclusions were based upon comparisons of sections of the pancreas of fasting dogs and pigeons with those of normal animals of the same species.

Marrassini (1) has claimed to produce, by means of prolonged hyperglycemia, hypertrophy of the islets and increase of fuchsinophile secretion-granules in their cells. Cell-division was never seen in the islets, but the acini in places seemed to be merging with and changing into islets.

Labbe and Thaon assert that guinea-pigs after a prolonged diet of meat show a remarkable proliferation of the islands of Langerhans. The diet was continued for 5 or 6 months. The acini showed no changes.

Laguesse (7), in his earlier experiments with fasting and subcutaneous dextrose injections in snakes, observed practically no changes in the islets. But in his later experiments (12, 14, 15) with pigeons, he finds a very pronounced increase in the number of islets, even to twice that in normal controls. On re-feeding,

the number of islets returns to normal. As there are signs of transition but never signs of degeneration or destruction of islets, he concludes that the changes are due to transformations between islets and acini.

Fischer's recent paper asserts that the number of islets increases noticeably in frogs and tritons that have fasted 3 or 4 months. When such fasting animals receive their fill of meat, the pancreas for the next few days shows only a few very small islets; after 17 days they have returned nearly but not quite to normal.

(b) Authors Announcing Negative Results.

Gianelli and Giacomini, likewise Massari, found no changes in the size or number of islets in lower species, in full digestion or after several months' starvation. Diamare also found the islets in cold-blooded animals unchanged by any functional condition of the pancreas; and in cats or rats, whether fully fed or dead of starvation, the islets were unaltered. Diamare (4) found dextrose injections in frogs without effect upon the islets. His previous work had shown that such injections in selachians do not alter the number of islets, but produce mitotic and karyolytic changes. These authors founded the doctrine of the unchangeability of the islets.

Harris and Gow asserted that the islet cells become smaller when the pancreas begins to discharge its juice, but did not mention numerical changes.

Jarotski subjected mice to inanition, or to diets of pure fat, starch or sugar. There were no islet changes except on sugar diet, when all the pancreatic cells, including those of the islets, were diminished in size. Under some conditions the acinar cells bordering the islets were much more granular than elsewhere, so that the author suggested the function of the islets to be the preparation of some mother-substance for the external secretion.

Hansemann was unable to confirm the statements of Lewaschew. He attributed the reported changes under different functional conditions to the changes in the acinar cells, which sometimes tended to obscure the islets, and sometimes brought them into better view.

Stschatsny [ref. by Ssobolew (2)], in an insane patient dead after 35 days starvation, "found the islets, in contrast to the digestive apparatus of the gland, very well preserved."

Ssobolew (2) performed experiments on various animals, by starvation with and without intravenous injection of dextrose, by carbohydrate diet, and also by extirpation of two-thirds of the pancreas followed by heavy carbohydrate diet and intravenous injections of dextrose. Changes in the number of islets were not observed; but the cells showed increased granulation during fasting, and diminished size and granulation after carbohydrate excess. The author concluded that the secretion represented by the granules is used in carbohydrate metabolism.

J. Lepine found no change in the islets from dextrose injections except a diminution of size and granulation, interpreted as a secretory phenomenon.

Schmidt observed no changes in the islets after extirpation of part of the pancreas or after injections of dextrose.

Fichera described changes in the granules and in the blood-supply of the islets in dogs at successive periods after feeding.

Aldheim [ref. by Lepine (1), p. 178] obtained negative results from feeding or injections.

Dewitt studied the islets in the glands of guinea-pigs, (1) in full digestion, (2) after different periods without food or drink, (3) after different periods of pure carbohydrate diet, (4) after periods of pure meat diet. Careful measurements and counts showed that the islets were unchanged in size or number. Variations between normal animals were as great as any shown by the experimental animals. She declared the so-called transition forms to be merely resting pancreatic tubules.

Tiberti (3) made daily intraperitoneal injections of dextrose in rabbits and guinea-pigs for 2, 3, or 4 months. There was no effect upon the islets.

Frugoni and Stradiotti gave dextrose to rabbits and guinea-pigs subcutaneously and by mouth, every day or every other day. The longest subcutaneous experiment was 66 days; the longest feeding experiment was 135 days. The doses were sufficient for glycosuria. There were no anatomical changes in the pancreas or elsewhere.

Bensley's investigation by the vital staining method has included the effects of several days' fasting in guinea-pigs and dogs. He finds that neither the number nor the size of the islets is altered.

Cecil (4) has starved dogs from 6 to 16 days, and has found no changes in the islets.

C. Miscellaneous Experiments.

In previous chapters, mention has been made of the hypertrophy of the islets claimed by Lorand after thyroidectomy, and of the pancreatic changes observed by Natus, Gilbert and others from portal stasis.

Cushing's book mentions the claims of authors concerning alterations in the islets and in the acinar cells adjoining them, in consequence of hypophyseal operations.

Scaffidi studied the effects upon the pancreas produced by section and stimulation of the vagus and sympathetic. Babkin, Rubaschkin and Ssawitsch observed the effects of stimulation of the vagus and sympathetic, and of the introduction of solutions of soap or HCl into the duodenum. Both these researches concerned essentially the acinar tissue, but doubtless any striking alterations in the islets would have been reported. Aside from the electrical stimulation experiments of Mankowski, these seem to be the only investigations of the effects of nervous influences, and it may be that a field of study concerning the islets is here open.

Fischer has claimed an immense increase of islets in the triton after extirpation of the spleen. The increase was still present 31 days after operation; whether it is permanent was not decided. Obviously, if by any means whatever an increase of islets could be produced with certainty, free from suspicion of erroneous observation, such a method would at once attract interest in connection with diabetes.

D. Isolation of Pancreatic Tissue.

The effects of ligation of the excretory ducts have been studied in various glands (*e.g.*, the bile-duct by Richardson, Tsunoda and others); but for no other organ has this investigation been so active as for the pancreas. Ligations of the pancreatic ducts have been performed for the study of the digestion and assimilation of food, of gland-atrophy in general, of retention cysts, of vicarious function of the digestive glands, of acute and chronic pancreatitis and fat-necrosis, and of diabetic problems. The impetus to the last-named investigation is given by the fact that ligation of the pancreatic ducts ordinarily leads to atrophy without diabetes, and thus information concerning the essential anti-diabetic elements of the gland has been sought from examination of such atrophic remnants.

The pancreatic ducts in the cat have been described by Herter, and in the dog by Revell; and Hess and Sinn have particularly described and emphasized the supernumerary ducts which are frequent in the dog. Simple ligation never blocks permanently the main pancreatic duct of the dog, and even when it is cut between ligatures its continuity may not infrequently be restored unless special preventive measures are employed. Hess has questioned such a restoration. But Claude Bernard observed it even after the ducts were injected with oil; it is said to have been observed by Bouchardat, De Domenicis, Pawlow and Smirnow, and Tiberti; Pratt, Lamson and Marks reported a probable case in a dog; it has been observed by Visentini and by myself in dogs, by Ssobolew (2) in dogs and cats, and by Dewitt in cats. Milne and Peters (1) have reported two striking instances in dogs. When the duct is restored, the atrophic gland-tissue largely recovers its structure and function. That these observations are not due to accessory ducts remaining unligated, is proved by the fact that authors from Ssobolew to the present have had no further trouble when they have taken the precaution of interposing mesentery between the cut ends of the ducts. In my experience, the lesser ducts do not regenerate like the main duct. Some of the earlier workers ligated the ducts after having injected them with some foreign substance, generally oil. Experiments with pancreatic grafts and transplants also require consideration in connection with this topic.

The earliest ligations of the pancreatic ducts, performed for digestive experiments, were not accompanied by microscopic examinations; or else the islets were not mentioned. The list of these earlier investigators comprises Bernard, Munk and Klebs, Pawlow, Schiff, Langendorff, Senn, Pawlow and Smirnow, Martinotti, Remy and Showe, Henry and Wollheim, and Rosenberg [for references see Schulze, Sauerbeck (2), and Abelmann]. Ribbert and d'Arnozan and Vaillard mentioned the presence of persisting structures which later authors have interpreted as islets; but it is perfectly possible that the opinion of d'Arnozan and Vaillard was correct, viz., that the structures were groups of acinar cells returning to an undifferentiated form. Treuberg is said by Ssobolew to have seen preservation of islets in one case. The earliest workers with diabetes made no reference to the islets. Minkowski, Thiroloix, Hedon and others described the progressive atrophy and sclerosis of isolated portions of pancreatic tissue left *in situ* or transplanted under the skin or elsewhere. Mouret described

in detail the changes occurring in the ligated pancreas and in subcutaneous grafts, and used the word "ilôts", but his reference was to areas delimited by fibrosis, not to islets of Langerhans.

This is a question in which a time-element is concerned to a certain extent; that is, the changes observed depend partly upon the length of time since operation. Nevertheless, in general, it is possible to consider the literature conveniently by dividing authors into four classes, as follows:

I. Authors reporting preservation of islet tissue only.
II. Authors reporting preservation of acinar tissue only.
III. Authors reporting preservation of neither tissue.
IV. Authors reporting preservation of both tissues.
V. Discussion.
VI. Observation of Minkowski.

I. Authors Reporting Preservation of Islets Only.

Vassale in 1889 is said to have described in detail the changes in both islets and acini following ligation of the pancreatic ducts in dogs and rabbits. In rabbits the acini disappeared and the islets persisted. The results in dogs were different.

Katz and Winkler, in studies concerning fatal fat-necrosis after ligation of the pancreatic duct in dogs, reported that the islets were preserved better than the remaining tissue. Only two of their animals lived as long as 8 days, and the statements concerning the islets have no great importance in the present connection.

Ssobolew (2) ligated the pancreatic ducts in 14 dogs, 12 cats and 27 rabbits, which were killed from 1 to 400 days after the operation. In 6 other rabbits the duct was cut and only the intestinal end ligated; the animals all lived, the peritoneum was uninjured, and atrophy of the remnant occurred just as when the pancreatic end of the duct was ligated. In 3 other rabbits the ducts were injected with oil before ligation; some fat-necrosis and necrosis of portions of the pancreas followed, otherwise the results were much the same as after simple ligation. In all the animals, the atrophy involved only the acini, and the islets remained absolutely normal. The acinar cells first begin to lose their granules and to take on a resemblance to the duct-cells; at certain stages a distinction between the two is impossible. The duct-cells degenerated, but multiplication of them also occurred by mitosis. The fibrosis is of interlobular character. At first

blood-vessels and nerve-fibres and -cells are abundant; their number later diminishes; it is suggested that the ganglia which disappear are those governing the external secretion. Atrophy is somewhat slower in the dog than in the rabbit; connective tissue formation is more active than in the rabbit, and proliferation of the duct-cells is less marked. In cats the process is more rapid and diffuse. In all species, a certain number of islets are at first destroyed by pressure of connective tissue, and others appear atrophic; but at later periods the author emphasizes the absolutely normal appearance of the islets in all species. In the rabbit 400 days after operation, the fibrous tissue has become atrophic or replaced by fat; all inflammatory processes are at an end, and the islets remain entirely normal. The author advances his findings as a support for his insular hypothesis of diabetes.

Schulze ligated off a portion of the pancreas in 18 guinea-pigs. Only a small fragment was thus isolated, in order that the pressure of retained secretion might be avoided. The animals were killed 3–80 days after operation. The usual sclerosis of the parenchyma occurred, but the islets showed not the slightest change in any particular. The author interprets his results strongly in favor of the insular hypothesis. His plates verify his claim of fully normal islets in the midst of fibrous tissue.

Sauerbeck ligated the pancreatic ducts in rabbits, and claimed that at about the 30th day no islets could be found, and the animals were glycosuric. Later the islets reappeared, and the glycosuria ceased. The announcement was made as a preliminary communication in 1904, and no further statement has followed.

Diamare in 1905 observed disappearance of most of the islets as well as acini after oil-injections of the pancreas in dogs. In 1908 he isolated the pancreas in frogs, and found the gland atrophied to a mere thread; a few acini were preserved, but the numerous large islets were the most striking part of the picture, which the author interpreted in favor of the insular hypothesis.

Tschassownikow ligated the ducts in rabbits and studied the changes at intervals up to 75 days. He found that the islets were preserved and the rest of the gland transformed into fatty tissue. He makes the valuable suggestion that some of the contradictory results of different authors are perhaps due to differences in technique.

Marrassini (1) divided the ducts in rabbits, some of which were then treated with dextrose injections. Autopsy showed the

pancreas mostly replaced by sclerotic tissue, and the acini rapidly disappearing. The islets were reduced in size and number except in those animals receiving dextrose injections; in these the islets remained medium size and the cells were full of fuchsinophile granules, found also in the nucleus. There were no mitoses in the islets, but an appearance of acino-insular transitions. At the end of 60 days the islets were still present, the health good and the dextrose tolerance apparently normal. The author favors Laguesse's idea that the rounded islets are permanent, while the irregular ones are formed from acini; and he suggests that certain stimuli may normally or abnormally cause mutual transformations of islets and acini.

Visentini (2) studied the pancreatic ducts in the dog and their restoration after resection. Visentini (3) found that when the duct is not restored, the pancreas atrophies completely, the acini all disappear, but the islets persist.

Gelle, a pupil of Laguesse, reported observations of acino-insular transitions in rabbits after ligation of the duct. In particular, he described the autopsy of a rabbit killed twenty-five months after operation. Nothing was left of the pancreas except the numerous islets amid a mass of fatty tissue; even the dilated ducts had disappeared.

Niemann ligated the ducts in dogs, and killed them within 1 or 2 months. There was rapid atrophy and sclerosis of the acinar tissue, but the islets persisted. Neither diabetes nor cachexia is mentioned.

Brugsch (2) reiterated Niemann's claims. He insists, contrary to Lombroso, that after ligation of the ducts really normal acinar tissue is never found. Extreme atrophy finally follows simple ligation. But (p. 353) the sclerosis is very rapid when vessels are also ligated. In one dog he ligated the ducts and also "sämmtliche zum Pankreas ziehenden Gefässe" [a loose statement; the complete ligation always causes prompt death from acute necrosis of the pancreas]. The dog lived somewhat more than a month, and died of marasmus. The pancreas was represented by a sclerotic cord.

MacCallum (2) ligated off about a third of a dog's pancreas in October, 1908. In May 1909 the non-ligated portion was extirpated; the ligated portion was completely atrophied, and appeared only as a faint opacity in the mesentery. There was a slight transient glycosuria, but later the dextrose tolerance was consider-

able. On June 1 the atrophied remnant was removed, and was found to consist of cells resembling those of the islets, though the possibility of altered acinar cells is not excluded.

Kirkbride undertook to verify MacCallum's results, and reported ligations in two guinea-pigs. One was killed after 3 weeks. The acinar tissue was found undergoing rapid degeneration and replacement by fibrous tissue, while the islets appeared normal. The other pig was killed after 15 months. There was found a cyst-like duct surrounded by fatty tissue; microscopically, no trace of acinar tissue, but islets perfectly preserved, with appearance and granulation indicative of full function. The findings in both animals were confirmed by the Bensley stain, and the colored plates support the assertions.

Finally, Laguesse has published a considerable series of observations in this field. With Gontier de la Roche in 1902 he described the processes in the guinea-pig pancreas at various stages after ligation. The acini quickly disappear; they and the ducts form first pseudo-cysts and then islets. Not only do new islets form, but the old ones grow by proliferation. At about the end of the second month the sclerosis begins to invade the islets; they grow smaller, many disappear, and the remainder show atrophic changes. This result is looked upon as merely secondary. Laguesse (9, 11, 16) worked especially with rabbits, and announced the transformation of the pancreas "into a pure gland of internal secretion." Young animals grew and thrived after the ligation; there was never glycosuria or disturbance of health. Some were examined 25, 37, and 45 months after operation. All traces of acini and ducts had disappeared, while the islets remained fully normal and, as usual, most numerous at the splenic end. As will be noted later, the findings in dogs were different.

II. Authors Reporting Preservation of Acinar Tissue Only.

Rosenberg in 1898 ligated the pancreatic ducts in a series of dogs. He states repeatedly that the stained sections of the atrophied glands showed complete replacement by fibrous tissue except for a few degenerating acini. In a few cases, small nodules of tissue showed better preservation than the rest. He makes no mention of islets, and in view of the early date, his work probably furnishes little evidence against their preservation.

Certain results with grafts require notice here. When bits of pancreas tissue were placed in the liver or spleen, Tiberti (3) found the usual central necrosis, but preservation of both acini and islets in the peripheral zone; while Ottolenghi concluded that the islets disappear very quickly by rapid necrosis. As will be noted later, Kyrle, by the pedicle method, found that transplants in the spleen showed degeneration and regeneration of both islets and acini. Pratt [(2); operation performed by Murphy] reported the autopsy of a dog six months after extirpation of the entire pancreas except a graft, by the pedicle method, implanted in the spleen. The animal was cachectic and the sugar-tolerance low; an abscess was found at autopsy; but in the spleen was found the living remnant of the pancreatic graft, containing unmistakable acini, some fibrous tissue, nerves and ganglion cells, but nothing resembling an island of Langerhans. No pancreatic tissue could be discovered elsewhere.

Milne and Peters (1) separated off the processus lienalis of the pancreas in 2 guinea-pigs, 6 rabbits, 5 dogs, and 12 cats, and studied the changes up to 5 or 6 months. In cats the atrophy was marked within 48 hours. The changes advanced, until within 13 weeks nothing was left but small clumps of atrophied acinar cells, somewhat resembling islets, but with duct-communications and intermediate formations demonstrating their acinar nature. In rabbits, atrophy was also prompt; islets can still be observed after 10 days; but after 2 months everything has disappeared except very atrophic acini and a few clumps of doubtful cells, distinguished as acinar by their peripheral situation in the lobules and their connections with atrophic acini. In dogs, the isolated portion of pancreas was found to atrophy to a thin fibrous strand, containing a few small nodules of persisting acinar tissue. Occasional solid clumps of cells resemble islets, but their development can be traced from atrophic catarrhal acini. The authors uphold the transition doctrine.

III. Authors Reporting Preservation of Neither Tissue.

Vassale, whose results with rabbits were mentioned under (I), found in dogs that when a duct is ligated, there is complete atrophy of the entire tissue of the area drained by that duct.

Hedon (1*A*) reported that simple ligation of the ducts in rabbits is not followed by glycosuria, and a little pancreatic tissue is

always found persisting. But when the ducts are injected with oil, there is generally a complete destruction of all pancreatic tissue. Most but not all such animals show glycosuria, sometimes intense, with corresponding hyperglycemia. Sometimes the glycosuria is irregular. It always ceases when starchy food is withdrawn, and it then fails to reappear when oat-feeding is resumed. These rabbits appear well, gain weight, and show the usual glycosuria after piqûre.

Sandmeyer produced the well-known form of diabetes named after him by extirpating most of the pancreas, leaving a portion separated from the bowel, with part of its vessels also ligated. Many months later, the autopsy showed the pancreas remnant reduced entirely to scar-tissue.

Mankowski repeated Schulze's guinea-pig experiments, by tying two ligatures about the pancreas near the splenic end, and examining the areas "before," "between" and "behind" the ligatures, from 3 to 40 days after operation. Only 6 pigs lived; the number that died is not stated. The results were stasis, gradual sclerosis, and disappearance of parenchyma. "Between" and "behind" the ligatures, the changes were so great that islets could not be distinguished from acini. "Before" the ligatures, where the outlet for secretion was still free, there was merely an irritation-fibrosis in the immediate neighborhood of the ligature; this process was resisted better by the islets than by the acini. The author considers the ligature-method without value for deciding the function of the islets.

Laguesse (6) found that a dog's subcutaneous pancreatic graft, removed 3 months after operation, was almost as large as originally, but showed great increase of connective tissue, atrophy of parenchyma, and fatty degeneration of the cells; and the changes in the islets were as marked as in the acini. The author considers the dog a less suitable animal than the rabbit for studying the changes following ligature. Lombroso (16) opposes this view.

Pende has found that the zymogen granules disappear from the acinar cells within 1 or 2 months after ligation of the ducts. The reaction to pilocarpin diminishes during the few days following operation, and disappears in about a week. The islets for some time show only slight changes, but at the end of a year they are almost completely atrophic. The few persisting ones are so changed as to be of doubtful value to the organism. The author

considers the absence of diabetes to be due to a gradual habituation of the animal to loss of the pancreas (both islet and acinar tissue). Of eight rabbits, only one showed glycosuria; this was present only for a few days at the end of the first month; it was absent during constant observation during the next two months. During the fourth month, subcutaneous tests showed the tolerance for dextrose to be practically nil, and a very small dose of adrenalin caused heavy glycosuria. The animal was killed at the end of the fourth month, and islets were found present, some normal and some changed. The author thinks that if the insular hypothesis were correct, the transient glycosuria and the continued low tolerance should not have been present.

Hess and Sinn have particularly opposed Lombroso, with regard to the consequences of duct-ligature, setting their claims of atrophy of the pancreas and deficient absorption of food against his claims of preservation of the pancreas and good absorption of food. They especially emphasize the difficulty of ligating all the ducts; in 7 experiments, they succeeded only twice in finding and ligating every duct.

Lombroso's results in rabbits have been opposite to his results in other species. With Sacerdote, he examined the tissue from 36 hours to 110 days after ligation. A remarkably rapid degeneration of the acini was observed; within 4 to 6 days after operation none remained normal. After 20 days the great majority of the acini have disappeared; but a few of them, greatly altered, persist to the end. At first there were numerous mitoses in the acini and occasionally in the ducts, but never any active regeneration. No mitoses were seen in the islets; they persist longer than the acini, but gradually diminish in number, and those remaining show abnormal appearance. Like Ssobolew, Lombroso finds that when the duct is cut and left opening freely into the peritoneum, the result is the same as when it is tied. When the ducts were injected with oil, considerable necrosis ensued, and there was difficulty in deciding whether the persisting cells were acinar or insular. Glycosuria was present in only a few out of 12 such animals; and was always below 0.5 per cent. Rabbits with atrophied pancreas were healthy, gained weight, and the females bore and reared young.

Carraro performed two sorts of experiments. In the first series, the greater part of the pancreas in young rabbits was destroyed by freezing; there resulted a marked hyperplasia of the

epithelium in the existing acini, which did not proceed to the formation of new acini. In adult rabbits the process is analogous but less extensive. The islets never participate in the regeneration; a partially destroyed islet does not restore its lost parts; any loss is replaced by scar-tissue. The second series dealt with duct-ligation. Here regeneration appeared slowly; heaps of epithelial cells were present, often showing zymogen granules; but regeneration did not proceed to the formation of new acini, and the whole was soon obliterated by scar-tissue. The islets of Langerhans took no part in the regeneration, but were slowly and gradually destroyed.

Opie [(4), p. 297] says, "Extirpation of tumors situated in the head of the pancreas is difficult and dangerous. Only part of the head of the gland can be removed, for obliteration of the ducts is followed by chronic inflammation of the parenchyma distal to the point of obliteration, and advanced sclerosis following occlusion of the pancreatic ducts is accompanied by fatal diabetes."

Pratt, Lamson and Marks, also Pratt and Spooner, describe almost total destruction of all pancreatic tissue after resection of the ducts in dogs.

Fischer, ligating off part or all of the pancreas in frogs, and examining at various periods up to 46 days, has found gradual disappearance of the entire parenchyma, the islet cells being no more resistant than the acinar cells.

IV. Authors Reporting Preservation of Both Tissues.

Hansemann tied a thick silk ligature about the middle of the pancreas in ten dogs. He reported that only a portion of the tissue behind the ligature is destroyed. The fibrosis is most marked in the neighborhood of the ligature itself; here the islets persist in areas where the acini are destroyed, yet many islets disappear. The author rejects the idea that the duct is essential to the existence of the gland, or that the islets alone survive. [He evidently did not produce a permanent closure of the duct.]

Zunz and Mayer [see also Zunz (1)] observed a rather rapid atrophy following ligation of the ducts in dogs. In 38 days the pancreas was reduced to half its size. Numerous large islets were found, but more or less acinar tissue was also preserved throughout; the longest duration of such experiments was fifteen months.

The usual dilated ducts and fibrous changes were present. Immediately after operation the dogs lost weight, but later regained it. There was never glycosuria.

Dewitt ligated off portions of the pancreas in cats, and examined the tissue from 18 hours to 197 days afterward. There was considerable mortality from inflammation or inanition. The islets in particular were well preserved, though appearing somewhat compressed by connective tissue at first. The acini and small ducts underwent degenerative changes, and the lobules were much compressed by interlobular connective tissue; but replacement by fibrous tissue was never complete, and the lobules always retained the appearance of lobules.

Herxheimer chose the chicken as a specially suitable animal for testing the alleged survival of the islets after ligation. He found that the parenchyma is well preserved, and that the supposed persisting islets are mostly new-formed from acini. The new islets are often five or ten times as large as the old. He considers that ligation experiments afford no support for the insular hypothesis; that the islets are not an independent tissue, but merely that form in which the pancreas-cells are most resistant and best fitted for internal secretion.

Tiberti (1, 2, 2*A*) found that after ligature of the duct in rabbits, the acini and ducts at first form small cysts. Some acini degenerate, the cells of others undergo de-differentiation, losing their granules and reverting to embryonic type. The author compares the behavior to that of other cells (muscle, kidney, salivary glands) after injury, also that of the liver-cells in cirrhosis. The de-differentiated cells then regenerate the specialized forms, and zymogen granules appear in them. In the first month or two, only atrophic acini are seen, but after $2\frac{1}{2}$ months there are normal-looking acini with zymogen granules. The total amount of such regeneration however is slight. The islets persist with certain changes, and contain capillaries. After 4–5 months, compact, sharply delimited groups of cells are visible, most numerous at the splenic end; some are practically normal islets, some changed islets, some of doubtful nature. The rabbits all remained in good condition and free from glycosuria, except two which were kept for 5 months; these emaciated and at the time they were killed showed glycosuria of 3 per cent. In dogs, Tiberti found the sclerosis less than in rabbits, and both islets and acinar tissue were preserved.

Kyrle studied the regenerative processes in the pancreas, by means of ligations of ducts and transplants into the spleen. The series included 80 dogs and 80 guinea-pigs. About a third of the gland, at either the splenic or the duodenal end, was ligated off, and the tissues examined at intervals, the longest being 40 days. Mitoses appeared both in the acini and in the peripheral portions of the islets. Giant islets were one result. But to a much greater extent, buds sprang from the ducts, and developed some into islets, some into acini. Transitions between islets and acini were never seen, and would be superfluous, since each can regenerate itself or be produced from the ducts. In the duodenal end, the buds from the ducts formed acini, seldom islets; in the splenic end they formed many islets. Grafts into the spleen were successful by means of a vascular pedicle, which was cut at a secondary operation. The regenerative processes were the same as in the tissue ligated *in situ*, but less pronounced, because of the poorer nutrition.

Lombroso's numerous publications deal exhaustively with the effects of ligation of the pancreatic ducts in several species. Lombroso (1, 3, 6, 9, etc.) asserts that when one lobe of a pigeon's pancreas is ligated off, the lumina of the acini enlarge, the epithelium changes from columnar to pavement, and there is rapid atrophy of the acini while the islets persist unchanged. But in about two months regenerative processes begin and restore practically the original condition of the tissue. If the entire gland is ligated off, the pigeon dies of cachexia in 10–18 days; likewise if one or two lobes are ligated, and the remainder ligated within $1\frac{1}{2}$ months thereafter, before the lobes first ligated have had time to regenerate. But by waiting 2 months, and thus giving the first lobes time to regenerate, the final ligation can be performed without disturbance of well-being. The author argues that since the pigeon dies of cachexia under conditions when the islets are intact but the acini degenerated, the acini must subserve some internal function. In dogs, the pancreas after ligation has sometimes quickly atrophied to a fibrous cord, but in most cases Lombroso has found only slight atrophy. In the average case, the connective tissue is somewhat increased, the ducts somewhat enlarged, and the acinar cells diminished in size but without signs of degeneration. The islets were generally normal, but in case of extensive fibrosis the islets suffer like the acini. Such dogs digest and absorb well, but generally fall victims to a severe marasmus

which causes death in 11 days minimum to 140 days maximum. Since the anatomical and functional results are so different in dogs, rabbits and pigeons, the author considers it unjustifiable to generalize from the findings in any one species.

V. Discussion.

As in all matters pertaining to the pancreas, the above findings concerning duct-ligation show no lack of variety. After comparing them, one is tempted to repeat Ssobolew's quotation from Goethe's Faust:

"Da steh' ich nun, ich armer Thor,
Und bin so klug, als wie zuvor."

But, as a matter of fact, the contradictions can at the present day be seen to be more apparent than real. Some of the differences depend upon species; for example, in guinea-pigs and rabbits the connective tissue seems to be less dense, there is a tendency to replacement of the ligated gland by adipose tissue, and in this soft bed many or most of the islets remain well-preserved indefinitely; but in the dog the scar-tissue is dense and hard, fatty change has never been reported, and ultimately islets as well as acini disappear by pressure. Some of the differences depend upon operative methods; after ligation of ducts the gland is especially sensitive to diminution of its vascular supply, perhaps because in the atrophic tissue the vessels become narrowed and tortuous, and blood is forced through them less readily; therefore when different investigators, or sometimes the same investigator, either sacrifice much of the blood-supply, or else attend carefully to its full preservation, the results are a rapid degeneration of parenchyma in the first case and a longer survival, with more or less regenerative attempts, in the second case. Other injuries, for example the injection of the ducts with oil, also hasten and intensify the tissue destruction, and the differences in degree in the hands of the same or different workers may be explained as due to the degree of pressure or the associated trauma of the injection. Some of the observed differences depend upon the length of time after operation; for example, Schulze's description and plates show persistence of the guinea-pig's islets in the midst of fibrous tissue, while Laguesse and Kirkbride describe and picture them in the midst of adipose tissue; but as explained by Ssobolew, Laguesse and Kirkbride, the fibrous change is first, the fatty change second-

ary. In the dog, there may be more or less preservation of both islet and acinar tissue for a longer or shorter time, but the ultimate result is probably always the disappearance of both. Some of the reported differences depend upon individual differences of observation and interpretation; accurate distinctions between islets and acini under abnormal conditions are here of the highest importance; the question of transitions may be left open, but what some have described as transitions may perhaps be interpreted as a proliferation from the ductules and centro-acinar cells. The latter process may be looked upon as demonstrated. It may be remarked that a number of authors have drawn an analogy between the pancreas and the liver in this regard; but according to Mallory the bile ducts can produce only duct-cells, not liver-cells; the analogy thus falls through, but without prejudicing the formation of pancreatic cells from the pancreatic ducts, especially since there are so many other differences between pancreas and liver. [It may be noted that since stoppage of the pancreatic duct does not produce identical results in different species, the same may possibly be true of stoppage of the bile duct.] Some of the reported differences depend upon technical errors, such as failure to obtain permanent closure of the ducts, by Hansemann and perhaps others. Here comes in the dispute between Lombroso and various opponents, Hess claiming that Lombroso failed to ligate all the ducts, and Visentini suggesting a restoration of the ducts in dogs and communications between the ligated lobes and other lobes in pigeons. This dispute seems now to be in the way of satisfactory settlement. Lombroso no longer maintains the extreme position which was expressed, or seemed to be expressed, in his earlier utterances (for example, the statement which Hess quotes against him, "Le pancréas ainsi opéré se montre à l'examen histologique très peu modifié."). Lombroso now insists only that, though rapid atrophy occurs in some cases, there is in many cases a preservation of fairly normal-looking acini as well as islets during even the longest periods of observation (fifteen months by Zunz and Mayer). He examined the specimens in which Hess had reported atrophy, and expressed himself as satisfied because they contained a few well-preserved acini. The illustrations presented by Lombroso [(16), pp. 62, 65, 67, 68] show decided increase of connective tissue in the dog, pigeon and especially the rabbit; and the pigeon-section is taken 100 days after ligation, *i.e.*, more than the two months specified

by Lombroso for complete restoration. Finally, some of the reported differences depend upon entirely unknown causes. Lombroso in particular must receive credit for having called attention forcibly to the fact that the results in dogs under apparently identical conditions may be widely different. Some show a quick atrophy, others a prolonged preservation of tissue; some die of rapid cachexia, others live for long periods [see Zunz and Mayer especially] with little or no impairment of health. In Lombroso's experience the anatomical and functional disturbances have been parallel, but others have not always found them so [see next chapter]. Some reason for these differences must exist somewhere, and the question arises whether it may lie in the nervous system or elsewhere.

The bearing of the various results upon the insular hypothesis may be summarized as follows. The results of duct-ligation furnish no positive proof for this hypothesis. It appears that in rabbits and guinea-pigs the pancreas may be reduced to nothing but islets, without diabetes; but true diabetes has never been produced in these animals by any method; it is not known whether they are susceptible to the condition, and there is the possibility that the duodenal glands or other organs may substitute for the internal as well as the external function of the pancreas.* In dogs, it has not yet been demonstrated by serial sections that the animal is free from diabetes at a time when nothing remains of the pancreas but islet-tissue; and even this demonstration would not rule out Herxheimer's idea, that the islets are not a tissue *sui generis* and have no monopoly of the internal function, but are merely that form of pancreatic epithelium which is most resistant and best fitted for internal secretion. On the other hand, the results of pancreatic isolation do not disprove the insular hypothesis. In rabbits, accurate tests of the dextrose tolerance are desirable in those animals in which, according to Laguesse and others,

* Marrassini (2) investigated the so-called duodenal pancreas of rabbits, which consists of tubules resembling those of the pancreas, distributed among the mucous and serous glands of the duodenum. He stated that after tying the pancreatic duct, the mucous and serous glands are found diminished, and the pancreatic sort increased, so that some sections look almost like pancreas tissue. Sacerdote [ref. by Lombroso (16), p. 71] considers that accidental individual variations suffice to explain the observed differences. In the paper of Pflüger (8), Nussbaum states that the duodenal glands could not functionate vicariously for the pancreas in the dog, for the structure is entirely different. Rosenberg found Brunner's glands unchanged after pancreatic atrophy in the dog. Thiroloix and Jacob have found the duodenal mucosa unchanged in diabetic dogs.

the islets survive the complete atrophy of the other parenchyma. Spontaneous glycosuria has been observed by Hedon, Sauerbeck, Tiberti, Pende, and Lombroso, but always in connection with procedures which destroyed most of the islets. In pigeons, the results of pancreas-ligation according to Lombroso have been cachexia rather than diabetes; death may be due to a disturbance of an absorptive or some other function; and it is in fact the chief contention of Lombroso that the acini furnish *an* internal secretion rather than that they furnish *the* internal secretion which most writers have in mind, viz., the specific substance necessary for carbohydrate metabolism. In dogs, the Sandmeyer type of diabetes occurs after disappearance of nearly the whole pancreatic parenchyma. Diabetes has never been observed in association with well-preserved islets. Absence of diabetes has never been observed in the absence of islets, with the single exception reported by Pratt (2).* This observation needs to be verified in other animals, on account of the possible existence of aberrant pancreatic tissue or other accidental factors in a single animal. The work of Kyrle has shown that grafts into the spleen are feasible on an extensive scale. Repetition of the experiment of Pratt and Murphy is needed not only because of the great importance in connection with the theory of internal secretion and because of the interest concerning the function and fate of pancreatic grafts, but also because of this observation concerning the islets. If in a series of animals successful grafts into the spleen should be proved free from islet cells by the Bensley or other suitable stain of serial sections, and if diabetes should follow ablation of the spleen under these conditions, it is obvious that the pure insular hypothesis must fall, and that at least some share in the internal function must be conceded to the acini. On the whole, however, the general weight of the experiments performed thus far favors the idea of the specific function of the islets in carbohydrate metabolism. In rabbits, the procedures which destroy most of the islets are accompanied by either spontaneous glycosuria or extreme lowering of the dextrose tolerance, while procedures which cause disappearance of the entire acinar tissue with preservation of most of the islets are not accompanied by glycosuria, and Marrassini's work seems to indicate a satisfactory dextrose tolerance. In dogs, diabetes has frequently been found absent when the

* In the tissues described and pictured by Milne and Peters, the existence of scattered islet cells cannot be ruled out with certainty.

scanty persisting tissue was so degenerate as to be of doubtful significance for either the acinar or the insular hypothesis.

VI. Observation of Minkowski.

On account of its unique importance, an observation of Minkowski [(6), p. 399] is here translated verbatim. It concerns a contrast between two dogs.

"In both dogs, portions of the processus uncinatus of the pancreas were transplanted under the skin, and after some time the remnant of pancreas remaining in the abdominal cavity was completely extirpated. In one dog, in which the subcutaneously implanted portion of the gland was approximately twice as large as in the other, the vascular connection of the processus uncinatus proved to be different from the normal, in that instead of one large, two smaller arteries supplied the distal end of the gland. In order to form a convenient pedicle, one of these vessels had to be ligated. The excretory duct of the transplanted gland-fragment was as usual brought out through the parietes, so that the external secretion of this fragment could flow out unbindered. In the second dog the vascular supply of the transplanted fragment was normal, but the fistula-formation from the excretory duct did not proceed smoothly. There was retention of secretion and marked transitory swelling of the gland-fragment. Later the flow of secretion was established, the gland-fragment diminished considerably in size, but was very plainly palpable as abnormally hard under the skin.

"After the removal of the remnant of the gland remaining in the abdominal cavity, there ensued after a few days in the first-mentioned dog a diabetes, which was at first of moderate and variable intensity, but which very quickly reached almost the same height as is observed after total extirpation of the gland. The quotient D/N rose on meat diet to 2.0–3.0. In the second dog, the gland-fragment present under the skin sufficed completely to prevent diabetes during the next two months, and only then did a slight glycosuria begin (up to 1 g. daily; D/N on meat diet = 0.1 – 0.2); and only after removal of the subcutaneous gland-fragment did diabetes appear in its full intensity.

"In contrast to this, the secretion of juice from the transplanted gland-fragment in the diabetic animal was much more abundant than in the non-diabetic. The relative content of the juice in trypsin (estimated by the method of Gross) as well as in diastatic ferment (by the Wohlgemuth method) varied in both animals within the same limits, but the amount of juice yielded by the diabetic dog was about seven times as great as by the non-diabetic.

"Also notable was the result of the anatomical examination of the subsequently removed subcutaneous gland-fragments. In the diabetic animal this fragment appeared almost normal; in the non-diabetic it was extremely shrunken and indurated. The microscopic examination in the case of the diabetic dog showed well preserved glandular parenchyma; in the case of the non-diabetic dog only sparse glandular lobules with greatly hypertrophied connective tissue. Very striking was the behavior of the islands of Langerhans in the two gland-fragments. Between the well-preserved glandular lobules of the diabetic dog it was necessary to search long, before the scanty remnants of the obviously shrunken and altered islet-cells could be found;

but, on the contrary, in the indurated tissue of the other gland-fragment, well-preserved Langerhans cell-groups could be found in almost every field."

Minkowski cautions against drawing conclusions from a single observation, but considers further experiments in this direction desirable.

Experiments.

The findings here reported concern primarily the pancreas but for the sake of completeness the entire autopsy is generally presented. For microscopic examination, the fixative solutions used in different cases have been formaldehyde, Zenker, Zenker without acetic acid, and alcohol 70 per cent. The routine stain has been eosin and methylene blue. All pancreas-sections have also been stained by at least one other method. In some cases this has been Mallory's anilin-blue connective tissue stain. Still more frequently the phosphotungstic acid hæmatoxylin stain has been employed; its usefulness for the present purpose consists entirely in the beautiful distinctness with which it brings out the secretion granules in the acinar cells; it does not show the granules of the islet cells. Numerous sections were also stained by the Bensley method; the results will be noted in connection with the individual animals. In certain instances it has assisted somewhat in determining the true nature of apparent transitional forms. Time has unfortunately not permitted decision concerning its merits for diabetic tissues. The importance of this point is recognized; but the proper study involves first a thorough mastery of the method, then a study of the normal dog, and finally a comparison between normal and diabetic dogs.* The carrying out of such a program was impossible. It has been necessary to draw conclusions essentially from the routine staining methods, and fortunately these have proved sufficient for the most important questions concerned.

Serial sections of an entire pancreas or pancreas-remnant have never been made. In the majority of the cats, examination of the pancreas has been on the basis of about ten sections cut from one block. In several cats and most of the dogs, there have

* Bensley and also Cecil (4) have observed the same types of cells and granules in the islets of the dog as in those of the guinea-pig. Milne and Peters (1) have found the method unreliable in dogs. The entire absence of granules from the islets of my diabetic dogs, except for a very few of them in Dog 167, may therefore be a significant observation, or may be due to unfamiliarity with the stain.

been at least twenty sections cut from two blocks, and in the more important diabetic animals there have been from three to five blocks of tissue with from six to ten sections cut from each. The tissue was ordinarily chosen from the body of the gland, especially since the remnants in diabetic animals were generally about the ducts. In case of a small remnant, the middle portion was sectioned for microscopic purposes; in case of a larger remnant, representative portions were chosen at intervals along its length. Ordinarily, every section was a cross section, frequently representing the full thickness of the gland or remnant. In some cases the duodenal wall has been sectioned with the pancreas; mention of it is omitted in the autopsies, since no changes were ever found in the mucosa or glands in diabetic or other animals.

The material may be roughly grouped in three divisions:

I. Injection and starvation experiments.
II Non-diabetic dogs.
III. Diabetic dogs.

I. Injection and Starvation Experiments.

The experiments performed with these animals are described in Chapters III and IV.

Cat 15.

Treated with subcutaneous injections of dextrose during many months; total duration of experiment 17 months. The autopsy findings were previously described. The feature of interest here is that the pancreas was found entirely normal, with no sign of change from the prolonged excess of dextrose. For adrenal, see Fig. 1.

Cat 21.

Cat 21, on full diet, received daily large subcutaneous injections of saccharose from June 17 to September 8. The autopsy was negative; in particular, the pancreas was normal as respects both acini and islets.

Cat 27.

Was starved from September 15 to October 16, while receiving daily subcutaneous injections of 3 g. dextrose per kilo, in 10 per cent solution. On October 16 meat was fed, but the cat was found dead the next day.

AUTOPSY.

Thyroid. — Gross and microscopic, normal.

Liver. — Gross and microscopic, normal.

Spleen. — Gross appearance small, normal.

Kidneys. — Gross and microscopic, normal.

Adrenals. — Macroscopically small. Microscopically, cortex normal; medulla shows exhaustion, viz., cells pale and vacuolated, with deficiency of cytoplasm and granulation.

Pancreas. — Macroscopically, exceedingly small. Microscopically, the phosphotungstic stain shows that most of the acini retain a few zymogen granules. There is simple atrophy of all the acini; the normal arrangement is mostly retained, but the cells have diminished to a low polygonal form, and accordingly the size of each acinus is greatly reduced. With the eosin-methylene blue stain, the cytoplasm of the acinar cells is seen to retain its basophilic character except in a few places. In such places, islets and acini merge without distinguishable boundaries. It is not justifiable on this account to assert a transformation of one into the other, for in view of the atrophy and decadence of the acinar cells, confusing pictures are unavoidable. The islets are not atrophic, but appear normal. The number in each microscopic field is markedly increased, but the apparent increase is easily accounted for by the diminished mass of acinar tissue.

Nervous System. — Dissected out entire and preserved in formaldehyde. The gross appearance was everywhere normal. Microscopic sections were prepared only from the cerebellum; these showed nothing abnormal.

Cat 29.

Was starved from September 15 to October 15, then bled to death when moribund. There was a daily subcutaneous injection of 3 g. dextrose per kilo in 80 per cent solution, and a final injection of 12 g. per kilo on the last day of life.

AUTOPSY.

Body greatly emaciated. A trifle of fat remains, under skin in groins, about kidneys, and in streaks along omental vessels. In omentum many pin-head white areas like fat-necrosis.

In the right pleura is 30 cc. clear watery fluid giving a heavy Benedict reaction. In left pleura, half as much similar fluid. Pericardial and peritoneal fluid little if any increased in amount.

Heart. — Small, flabby, empty.

Lungs. — Gross and microscopic, normal.

Thyroid. — Gross and microscopic, normal. Follicles distended with colloid.

Liver. — Slightly below normal size; normal appearance and consistency. Microscopically, normal, with considerable fatty infiltration.

Spleen. — Gross appearance small, normal.

Kidneys. — Gross appearance normal. Microscopically, nuclei stain perfectly; cytoplasm, especially of tubules, extensively vacuolated; no casts.

Adrenals. — Macroscopically rather small. Microscopically, cortex normal. Medulla shows picture of exhaustion; cells vacuolated; cytoplasm and granulation deficient.

Pancreas. — Different from Cat 27. Macroscopically large, firm, vigorous appearance. Microscopically, acini in most places show considerable zymogen. Everywhere mingled with the well-preserved acini are others showing more or less exhaustion, till in the extreme type the regular arrangement of cells is lacking; the cells themselves lose first their zymogen, and then their basophilic substance, so that the result is a considerable number of undifferentiated cells, small, polygonal, not recognizable as acinar cells except by the transitional forms between them. The undifferentiated cells are scattered irregularly through the parenchyma, not in the form of islet-like areas. In the sections examined, islets were relatively scarce, but probably within normal limits. Their cells show some deficiency of cytoplasm; the changes are not out of proportion to those observed in the acini. Transitions between islets and acini are absent.

Muscle of Leg. — Normal microscopically.

Bone and Marrow of Femur. — Normal microscopically.

Nervous System. — Dissected out entire and preserved in formaldehyde. The gross appearance was everywhere normal. Sections from the spinal cord at different levels, including the nerve-roots, showed nothing abnormal.

Cat 30.

Was starved from September 15 to death on October 18, while receiving daily subcutaneous injections of 3 cc. cottonseed oil per kilo.

AUTOPSY.

Body extremely emaciated. No true fat discoverable.

Heart and Lungs. — Negative.

Thyroid. — Gross and microscopic, normal. All follicles distended with colloid.

Liver. — Unusually small, and a peculiar brown color. Normal consistency. Microscopically, the staining is very irregular; nothing definitely abnormal.

Spleen. — Macroscopically small, normal.

Kidneys. — Small. Microscopically normal.

Adrenals. — Small, normal-appearing. Microscopically, cortex normal; slight picture of exhaustion in medulla (pale, vacuolated cells), but far less than in most of the starved cats.

Pancreas. — Very small, consistency firm. Microscopically, extreme alterations. The lobular arrangement is preserved, but only in a few places can an acinar grouping of the cells be distinguished. There is a universal return to undifferentiated type; in most areas the tissue under high power is not recognizable as pancreas tissue. Secretion is not visible except with the phosphotungstic stain; this shows that some cells retain a few typical zymogen granules; but a large proportion of the cells are entirely empty of secretion. The general type of cell is small, polygonal or rounded, roughly resembling islet cells, except for the deep-staining nuclei and the heavy (slightly basophilic) stain of the cytoplasm. No island of Langerhans can be positively distinguished anywhere, presumably on account of the extensive changes in all cells; but occasional small lighter-stained areas probably represent islets. This is perhaps the type of picture seen by those authors who have reported transformation of entire lobules into islet-tissue; but such a description in this case is certainly erroneous.

The illustrations depict fields chosen practically at random; the entire gland presents this appearance. Fig. 3 shows the altered size, form and arrangement, and poorly staining character of the cells. Fig. 4 shows the unequal distribution of zymogen granules. Some fields contained more zymogen than this one, others almost none. The autopsy was immediate. Focussing shows every granule to be of shot-like distinctness. Post-mortem change is therefore not an explanation.

Nervous System. — Dissected out entire and preserved in formaldehyde. Gross appearance everywhere normal. No microscopic examination.

Cat 31.

Was starved from September 15 to death on October 16, without other treatment.

AUTOPSY.

Ordinary picture of starvation; no trace of body-fat.

Heart and Lungs. — Negative.

Thyroid. — Gross and microscopic, normal. Follicles well filled with colloid.

Liver. — Gross and microscopic, normal.

Spleen. — Gross appearance small, normal.

Kidneys. — Small. Gross and microscopic, normal.

Adrenals. — In gross, normal. Microscopically, cortex normal; medulla shows some exhaustion, but much less than in certain other animals of this series.

Pancreas. — Changes of similar nature but not quite so extreme as in Cat 30. Great differences between lobules, and especially between different acini of the same lobule. Some retain approximately normal appearance and are fairly well filled with zymogen. The other extreme is represented by cells empty of zymogen, sometimes visibly arranged as acini and sometimes not; these cells are small, rounded or polygonal, poorly differentiated. All gradations between these two extremes are present. No islets or pseudo-islets are seen, presumably because of the extensive changes in all the cells. But the opaque, deep-staining nuclei and cytoplasm of even the most altered acinar cells distinguish them from typical islet cells.

Nervous System. — Dissected out but not preserved. Gross appearance normal.

Cat 32.

Was starved from September 15 to death on October 12, while receiving daily subcutaneous injections of 3 g. saccharose per kilo in 80 per cent solution.

AUTOPSY.

Ordinary appearance of starvation.

Heart and Lungs. — Negative.

Thyroid. — Gross and microscopic normal.

Liver. — Gross and microscopic, normal.

Spleen. — Gross appearance small, normal.

Kidneys. — Gross and microscopic normal.

Adrenals. — Cortex normal. In medulla, exhaustion is only moderate; some cells are deficient in cytoplasm, others retain the normal staining and granulation.

Marrow of Femur. — Normal.

Nervous System. — Dissected out entire and preserved in formaldehyde. Gross appearance normal. No microscopic examination.

Pancreas. — The characteristic changes of inanition are well-marked but not extreme. Acini are relatively well preserved, some of them fairly normal in appearance; nevertheless large numbers everywhere are returning to primitive type. In some cells not only the zymogen but also the basophilic substance seems lost. Islets are normal in number and appearance. These sections serve to explain why, in some animals, the islets may not be found in extreme starvation; for here some islets are perfectly distinct, others are beginning to lose distinctness on account of the poorly differentiated acinar cells which crowd upon them from all sides. Pictures of apparent transition are numerous, and fully bear out the descriptions given by Laguesse. Almost every islet seems to be merging into acinar tissue, with hardly a possibility of decision as to which cells are which. In general, however, it remains true that islet cells appear differently from undifferentiated acinar cells; the latter are distinguished by the relative darkness and opacity of their nucleus and cytoplasm. Even along the most confusing border-zones, it is generally possible by sufficiently careful study to recognize the two types of cells.

Fig. 2 shows such a border-zone of an islet. The size and shape of the cells suggest various stages of transition of acinar into islet tissue. The cells in the upper corners especially approach the islet type. Close observation shows that an actual transformation never occurs. The camera brings out the distinction even a trifle better than the eye. It is suggested that those who find apparent transitions should photograph their tissues.

Notwithstanding the extensive alterations, there is no increase in either the number or the size of the islets, and no changes in the acinar cells bordering the islets different from the changes in the acinar cells elsewhere. Therefore, the mere fact that there are occasional border-zones in which accurate distinctions are almost impossible, on account of the extreme changes in the cells, seems entirely insufficient evidence for assuming a transformation of acini into islets. If the acini bordering the islets are changing

into islets, those remote from the islets must be doing likewise, for the changes are the same. But as a matter of fact the islets retain their characteristic grouping and capillary arrangement. The acinar cells, though they may seem to lose their acinar arrangement, never assume an islet grouping nor show a capillary network. Accordingly this pancreas, which presents some appearances like transitions, also furnishes evidence to show that the apparent transitions are not real.

Cat 33.

Was starved from September 15 to October 12 without other treatment, then starvation continued till October 15 with daily subcutaneous dextrose injections. From October 15 to December 29 there was full feeding; but though the appetite was ravenous, the cat remained emaciated. [See Chapter IV.] It was bled to death on December 29.

AUTOPSY.

Emaciated, almost as in advanced starvation.

Thyroid. — Gross and microscopic, normal.

Parathyroid. — Microscopically normal.

Liver. — Gross and microscopic, normal.

Spleen. — Gross appearance normal.

Kidneys. — Gross and microscopic, normal.

Pancreas. — Gross and microscopic, normal.

Adrenals. — Gross appearance normal. Microscopically, cortex normal; medulla shows the exhausted appearance (vacuolization, great diminution of cytoplasm and granulation) characteristic of advanced starvation. A causal relation between the adrenal findings and the cat's general condition cannot be positively asserted, because this is the only animal receiving such treatment or showing such a condition.

Cat 36.

Was starved from September 16 to October 13, while receiving daily subcutaneous injections of 30 cc. 0.85 per cent NaCl solution per kilo. Feeding begun, but cat found dead October 15.

AUTOPSY.

Advanced emaciation. No visible fat, but a sprinkling of tiny white flecks like fat-necrosis in the omentum.

Heart. — Negative.

Lungs. — Simple congestion.

Thyroid. — Gross appearance normal.

Liver. — Gross and microscopic, normal.

Spleen. — Gross appearance normal.

Kidneys. — Gross and microscopic, normal.

Adrenals. — Cortex normal. In medulla, the picture of exhaustion, typical of advanced starvation, is present but not extreme.

Pancreas. — The organ has failed to respond to the feeding of the past two days. The changes of advanced starvation are still present. Secretion is almost absent. The shrunken cells, mostly retaining their basophilic character, are packed closely together, so that an acinar arrangement is frequently hard to distinguish. Islets are normal in number and appearance. Owing to the changes in the adjacent acinar cells, transition-pictures are inevitable, in the sense that routine stains reveal no exact demarcation. The obvious differences between acinar and islet tissue, and the absence of increase in the number or size of the islets, indicate that even in this extremely changed pancreas there has been no real transformation of elements.

Cat 43.

Was starved from September 28 to death on October 12, while receiving daily subcutaneous injections of 3 g. lactose per kilo in 80 per cent solution.

AUTOPSY.

Extreme emaciation. No fat.

Heart and Lungs. — Negative.

Thyroid. — Gross and microscopic, normal.

Liver. — Gross and microscopic, normal.

Spleen. — Small, gross appearance normal.

Kidneys. — Gross and microscopic, normal.

Adrenals. — Cortex normal. Medullary cells show the picture of exhaustion usual in advanced starvation.

Pancreas. — The usual inanition changes. Most of the cells have lost zymogen; there is the usual irregularity in this respect, cells full of granules occurring among other cells which are entirely empty. Some lobules also show considerable secretion, while others contain almost none. There are also the usual changes in the size and shape of the cells, but the basophilic character is mostly retained. The islets are normal in number and appearance. Transitional forms occur, but are few; the staining is

fortunate, in that islet cells are generally plainly distinguishable from the altered acinar cells lying beside them. In some places one or several altered acini have fallen together in an islet-like form, but distinction from true islets is generally possible. The general impression is against any transformation.

Cat 57.

Was starved from December 5 to 24 without other treatment, then starvation continued to December 29 with daily subcutaneous injection of 3 g. dextrose per kilo. There was marked ataxia. Death occurred on December 29 from injection of 2 g. calcium chloride.

AUTOPSY.

Fairly good bodily condition. Moderate amount of fat in the usual depots. Abdomen contains apparently nearly all the injected fluid, unabsorbed. No hemorrhage or sign of traumatism.

Heart and Lungs. — Negative.

Thyroid. — Gross and microscopic, normal.

Parathyroid. — Microscopically normal.

Liver. — Weight 78 g. Gross appearance normal. Microscopically normal, and contains considerable fat. A portion boiled immediately with KOH gave heavy qualitative tests for glycogen.

Muscles. — Appearance normal and vigorous. A specimen from the thigh was normal on microscopical examination. Muscle-tissue from different parts of the body, to a total weight of 60 g., was boiled fresh with KOH, and qualitative tests indicated a rich glycogen-content.

Spleen. — Gross and microscopic, normal.

Kidneys. — Gross and microscopic, normal.

Adrenals. — Cortex normal. The usual picture of exhaustion in the medulla.

Pancreas. — Gross appearance plump, pinkish, not atrophic. Microscopic. — Acini in fairly good condition. The majority contain secretion, sometimes in considerable quantity. Numerous acini also show the usual changes of inanition, even to the extent of complete loss of zymogen, and the dwindling of their cells to the usual small, poorly differentiated form. Positive, unmistakable islands of Langerhans are entirely absent (20 sections, 2 blocks). Long search reveals a few small areas which are probably

islands, and which probably explain the difficulty in finding them. They appear as if tightly compressed by the acinar tissue; the typical arrangement is therefore lacking, and the cells, though apparently normal, are so closely crowded as to be distinguished with difficulty, especially since the acinar cells pressing against them are frequently of the exhausted, poorly differentiated type. The appearance might well be the result of some circulatory or other accidental condition.

Nervous System. — Was dissected out entire and preserved in formaldehyde. Gross appearance normal. Sections representing the cervical, thoracic and lumbar cord and the corresponding nerve-roots were studied microscopically, and showed nothing abnormal in either cells or tracts.

Cat 59.

Was starved from December 5 to 15 with daily subcutaneous injections of 2 g. dextrose per kilo, then starved December 16–23 without injections, then December 24–30 with daily injections of 2 g. dextrose per kilo. On December 31 there was a subcutaneous injection of 6 g. dextrose per kilo; on January 1 a similar injection was given and the cat bled to death 6 hours later.

AUTOPSY.

Sites of recent injection show usual appearance; no infection. Body-fat abundant; fair amount subcutaneous; large masses in groins; intercostal muscles layered with fat; very abundant fat in peritoneal cavity; omentum and mesentery full of fat, and kidneys are almost buried in it. No fluid accumulation in any cavity.

Heart and Lungs. — Negative.

Thyroid. — Gross and microscopic, normal.

Liver. — Weight 95 g. Bright yellow with fat, and oily on section. Microscopically normal, except every cell loaded with fat in extreme degree.

Spleen. — Small, normal gross appearance; weight 5 g.

Kidneys. — Combined weight = 24 g. Gross and microscopic, normal.

Adrenals. — Small and flattened. Microscopically, cortex normal. Signs of exhaustion in medulla, much less marked than in cats which fasted longer.

Pancreas. — Unusually small; weighs only 1.9 g. Pinkish color, firm normal consistency. Probably a naturally small organ,

for microscopic examination indicates no advanced atrophy. Acini are mostly normal and generally well filled with secretion. A minority show inanition-changes, generally not in extreme form. Islets are normal in number and appearance. Also, altered acini in places appear to form pseudo-islets. Appearances of transition are very numerous and deceptive; the question is solely of interpretation. If there were really such an active transformation of acini into islets or vice versa, there should be marked changes in either the size or number of the islets; but such changes are not observable. The confusing border zones are readily explained by the numerous atypical acinar cells; where these occur scattered through the acinar tissue they cause no difficulty, but where they occur on the border of an islet, exact demarcation is difficult.

Thigh-muscle. — Microscopically normal.

Nervous System. — Dissected out entire and preserved in formaldehyde. Gross appearance normal. Stained sections of the cervical, dorsal and lumbar cord and corresponding nerve-roots, normal.

Cat 71.

Was starved from February 13 to March 2 without injections, then starved from March 2 to 19 with daily subcutaneous injections of 100 cc. 10 per cent glucose. Feeding was begun March 20, but the cat died on March 22.

Autopsy.

Emaciation as usual.

Viscera all negative in gross appearance.

Pancreas. — Weight 2.6 g. Microscopically, the usual inanition-changes are found. The number of resting in proportion to secreting acini is greatly increased, and the non-secreting cells are small, rounded or polygonal, lacking in distinct acinar arrangement. Some lobules are changed far more than others. Islets appear normal. Some confusing transitional forms are present, but the usual explanations probably apply.

Cat 171.

Was starved May 27 to June 10 without injections, then June 10–13 with daily subcutaneous injection of 3 g. dextrose per kilo. On June 14 the cat received a subcutaneous injection of 10 g. dextrose per kilo, and was bled to death $2\frac{1}{2}$ hours later.

AUTOPSY.

Emaciation not maximum. Some fat still present.

Thyroid. — Gross appearance normal.

Liver. — Small; normal color and consistency. Weight 53 g. Microscopically normal. Fat-droplets in cells are small.

Spleen. — Appearance shrunken, consistency firm; weight 2.5 g.

Kidneys. — Small; pale cortex, dark red medulla. Combined weight = 18 g. Microscopically normal.

Adrenals. — Microscopically, cortex normal, medulla almost so; very slight appearance of exhaustion.

Pancreas. — Practically normal. Weight 5 g. Microscopically, very little sign of inanition. Acini mostly retain normal form and are fairly well filled with zymogen granules. Islets fully normal in number and appearance.

Summary.

1. *Concerning Adrenals.* — The observation of Venulet and Dmitrowsky in starved rabbits appears to be confirmed in starved cats; *i.e.*, the adrenal medulla shows the microscopic picture of exhaustion. At the same time, the opinion of Luksch appears correct, viz., that the adrenal change occurs only in extreme starvation, and is the result rather than the cause of the cachexia. Thus, in Cats 59 and 171 it was far less marked than in those that fasted longer. The change is probably of no greater significance than the atrophy occurring in other organs, which was ignored in classifying them as "normal."

2. *Concerning Pancreas.* — The findings have not been identical nor followed any uniform law in all animals. Inanition is generally characterized by considerable loss of zymogen and diminution in size of the acinar cells; these changes may be extreme, and result in an apparently poorly differentiated form of cell. With occasional exceptions, distinctions between acinar and islet cells are always possible with the ordinary stains. Islet-pictures suggestive of those described by various authors have been encountered. In some instances, the number of islets per microscopic field has been decidedly increased; this has been due to the diminished mass of acinar tissue. In other instances, entire lobules (and in Cat 30 the entire pancreas) consisted entirely of small cells somewhat resembling islet cells and without visible

acinar arrangement. But in these animals the altered acinar cells were still recognizable as such; there was no transformation into true islet cells. In some instances no islets at all were visible, but the picture can probably be explained by a collapse of the islet capillaries and close crowding of the islets by altered acinar tissue. Pictures of apparent transition between islets and acini, as described by Laguesse, have been frequently encountered. Other evidence, noted in passing, leads to the opinion that the apparent transformations are not real, and that genuine transformations between islets and acini are not demonstrable under the above experimental conditions.

II. Non-Diabetic Dogs.

The following two dogs were in the laboratory for about 8 months, and during this time received occasional injections of various sugars in connection with various experiments [mentioned in previous chapters]. Each dog also went through a phloridzin period.

Dog 18.

Death from consequences of Bernard puncture.

Autopsy.

Liver. — Gross and microscopic, normal.

Kidneys. — Gross and microscopic, normal.

Adrenals. — Gross appearance small and shrunken. Cortex is normal. Medulla shows the typical picture of exhaustion following piqûre, viz., deficient chrome-staining, cells vacuolated, with absent granulation and scanty cytoplasm.

Pancreas. — Gross and microscopic, normal. In particular, the islands of Langerhans are fully normal in size, number and appearance.

Dog 21.

Death from peritonitis after partial pancreatectomy. Examination of the tissue removed at operation shows the following.

The pancreas is normal or slightly diminished in size. Its form is normal, and the parenchyma of normal consistency. Scattered through its tissue are areas of transparent, gelatinous appearance. These are small and infrequent in the processus lienalis, more abundant in the corpus. Especially the processus uncinatus is replaced by this transparent tissue throughout a

third or a half of its mass; larger and smaller areas of normal and abnormal tissue alternate. The transparent tissue is oily on section, and floats in water, therefore is presumably fat-tissue.

The gross are confirmed by the microscopic findings. Large areas of pancreatic parenchyma are free from fat; in some places it appears in the form of a few lobules, as if replacing one or two lost acini; elsewhere larger areas of fat are seen, sharply bordered by pancreatic parenchyma; and in other places the pancreatic tissue is entirely replaced by fat-tissue, with the exception of ducts and an occasional small cellular area.

In the pancreatic tissue, many of the acini are fully normal in all respects, and crowded with zymogen granules. All possible stages of transition are seen between these and other acini which have lost all appearance of secretion. In the latter type, the cells have become small and polygonal, a definite acinar arrangement is frequently not distinguishable, and accordingly, appearances of transition between acini and islets are numerous. This tissue was stained by all the methods mentioned, and there seems little doubt that the relations between acini and islets are fully normal. The islets are certainly normal in size, number and appearance. The impression of transition forms arises from the alterations mentioned in numerous acinar cells, but careful study suffices to make the distinction.

Out in the midst of the fatty tissue are seen the ducts and the small, isolated cellular areas already mentioned. The first impression is that these areas are islands of Langerhans. Closer examination shows that the cells, though resembling islet cells, have an acinar arrangement, and in some groups retain a slightly columnar form. The areas therefore consist of decadent acinar tissue, resembling islets in some places, but yet distinguishable.

Fig. 5 shows the various changes as well as can be done by one field. There is the sharp border line of pancreas-tissue and lipoma, the unequal distribution of zymogen granules, the normal contour of most cells, and the presence of a few shrunken empty cells, though this decadent type are much fewer here than in some other areas.

The conclusion from Dogs 18 and 21 is that the eight months of life under laboratory conditions, with occasional sugar-injections, failed to produce any specific changes in the pancreas. On account of the fully normal findings in Dog 18 and other injected animals, the condition in Dog 21 cannot be regarded as anything

but an accidental lipomatous change, with no demonstrable relation to the injections.

Dog 24.

December 27, removal of pancreatic tissue weighing 10.2 g. Remnant about lesser duct estimated at 1 g. All ducts ligated.

February 23, chloroformed after slow decline, due apparently to poor utilization of food and refusal to eat pancreas. No diabetes at any time.

Autopsy negative. Pancreas remnant reduced to a small atrophic nodule.

Microscopic Examination of Pancreas-remnant. — The usual scar-tissue is present, but fibrous changes through the parenchyma are surprisingly slight. The acini are well-preserved and full of zymogen granules. Islets are normal; they are few and small rather then many and large, and appear as if compressed somewhat by the acini, but yet are entirely within normal limits, and their cells appear normal.

Dog 32.

February 14, removal of pancreatic tissue weighing 12.4 g. Remnant about lesser duct estimated at 1.8 g.

Dog lived in good condition till May 15; then, on account of suspicion of distemper, was used for a fatal experiment with intravenous oil injection. There was no diabetes at any period, and various tests showed a considerable dextrose tolerance.

Autopsy, May 15, showed that the pancreas remnant had accidentally been shut off from the bowel, and was atrophied to tiny nodules. Other organs negative.

Microscopic Examination of Pancreas Remnant. — The small nodules are separated by fibrous tissue, but the parenchyma in each is well preserved. Acini are mostly normal and full of zymogen granules. A minority of them show a return toward primitive type. Islets are also normal in appearance, and their size and number is normal as compared with the acinar tissue. There is no selective destruction or preservation of either form.

Dog 73 (see protocol).

August 28, a loop of picture-wire was passed loosely about portal vein, with ends protruding outside abdomen. Diabetes insipidus followed.

October 11, splenic end of pancreas was removed, and the dog died in collapse the next day. Autopsy negative. No infection.

Microscopic Examination.

Liver. — Very decided thickening of fibrous trabeculæ accompanying branches of portal vein everywhere. Otherwise entirely normal.

Spleen. — Normal. No congestion or fibrosis.

Kidney. — Normal.

Adrenal. — Normal.

Pancreas. — Veins are visibly distended. No fibrosis. Acini and islets all beautifully normal. The former are full of secretion granules. The latter are large and numerous, apparently increased, but the prominence is probably due largely to the state of the capillaries, which are mostly dilated and full of blood. No transition forms. See Fig. 6.

Dog 74.

August 19, removal of five-sixths of pancreas (portion removed weighed 11.5 g.; remnant estimated at 2.3 g.). Used for various experiments. October 20, dissection about remnant. November 9, Bernard puncture. November 14, removal of 0.6 g. pancreatic tissue. November 23, Bernard puncture again. November 27, removal of 0.35 g. pancreatic tissue. December 3, found dead.

Autopsy showed low-grade peritonitis. Viscera negative. Pancreas-remnant weighed 3.2 g.

Microscopic Examination of Pancreatic Tissue.

A. Tissue removed at operation November 14. Fibrosis insignificant. Islets and acini normal.

B. Tissue removed at operation November 27. There is much scar-tissue about the fragment, which is also invaded by inter-acinar fibrosis. Some acini are normal, others in different stages of degeneration. Islets appear somewhat fewer than before; the fibrous tissue in them is distinctly increased, but the cells retain their normal arrangement and appearance.

C. Tissue from remnant found at autopsy. Slight post-mortem changes are present. Fibrosis and destruction of parenchyma have advanced; all the acini are surrounded. Some acini remain normal, but most are in various stages of degeneration. Islets cannot be discovered with certainty. Certain structures may represent their fibrous remains, containing a few cells. Pseudo-islets are very numerous. These consist of degenerating

acinar cells, which form groups at first suggestive of altered islets. But the true islet arrangement is always lacking; there is no capillary plexus nor fibrous reticulum; the cells are frequently larger than islet cells, and the dark, solid-looking nucleus and opaque, heavy-staining cytoplasm are entirely different from true islet cells. Naturally, all stages of transition are found between acini and these pseudo-islets.

The apparent absence of islets makes it impossible to distinguish the above tissue from diabetic tissue. The following considerations apply to this point. First, certain facts in the clinical record indicate that the animal was perhaps diabetic, but glycosuria prevented by cachexia. At least, diabetes levis was present. Second, the pancreas remnant was not sectioned serially; there is a little postmortem change; and the tissue is so disorganized by fibrosis and there are so many degenerative changes, that a considerable number of functionating islet cells might possibly be present and escape notice.

Dog 95.

September 26, removal of 16.1 g. pancreatic tissue. Remnant communicating with lesser duct estimated at 1.45 g., and a tiny clump about main duct, weighing 0.2 g. There was no glycosuria, but a marked polyuria and rapid cachexia. Bernard puncture on October 8, followed by death. Autopsy negative.

Microscopic Examination of Principal Pancreas Remnant. — Remarkably extensive fibrosis is present. The rapidly proliferating connective tissue everywhere cuts up the lobules and the acini, throwing the cells into confusion. Many acini still remain intact but separated from their neighbors. The cells of these, and most of the disarranged acinar cells, are full of zymogen, and cytoplasm and nuclei retain typical form, appearance and staining. But a considerable number of cells are returning to poorly differentiated type.

No islets can be distinguished. A distinction from those diabetic cases in which islets are absent is therefore impossible, but it may be remarked: (1) Sufficient pancreatic tissue was removed to cause diabetes, and it is possible that the dog was actually diabetic, but cachexia prevented glycosuria; (2) The general confusion in the tissue is such that numerous islet cells might exist unrecognized; if the islets were broken up like the acini, nothing but some remarkably selective stain could distinguish the cells.

Dog 97.

September 27, removal of pancreatic tissue weighing 26.9 g. Remnant about lesser duct estimated at 2.6 g. Very mild diabetes levis resulted. November 6, dissection about remnant. November 14, Bernard puncture, followed by four days glycosuria on meat diet. November 24, puncture again. December 1, found dead. Glycosuria preceding death.

Autopsy. — Liver fatty; other organs negative. Pancreas remnant found to be mostly isolated from bowel. Only 0.2 g. secretes into bowel; the remainder is extremely atrophic.

Microscopic Examination of Pancreatic Tissue.

A. *Isolated, Atrophic Remnant.* — The mass consists chiefly of fibrous tissue, in which are contained numerous distended ducts. The areas of parenchyma are also extensively fibrosed; the acini are separated; some are fairly well preserved, others breaking up and degenerating. Positive islets cannot be distinguished, though certain structures might be interpreted as representing altered remains of islets.

B. *Small Remnant Communicating with Bowel.* — The little nodule consists chiefly of connective tissue, in which are buried several small areas of parenchyma. These areas are relatively free from fibrosis, and the acini are mostly normal and full of zymogen. No islets can be distinguished.

This is another example of inability to distinguish from diabetes, because of the apparent absence of islets. The same reasoning applies as in other instances. Here, the larger, atrophic remnant may be considered the efficient agent in preventing diabetes. Its character is similar to that described by numerous authors, in dogs free from diabetes, with no islets discoverable in the atrophic pancreas-remnant. That they are not discoverable does not prove that they are not present. The acinar cells are sufficiently large and characteristic, that they are recognizable even when scattered and degenerating. If the islets are as badly disorganized as most of the acini in these sections, and the cells changed even in smaller degree than the acinar cells, the islet cells would be indistinguishable as such. In such specimens, it cannot on the one hand be asserted that the islets remain intact while the acini degenerate, nor on the other hand that no islet tissue is present.

Dog 148.

November 16, removal of pancreatic tissue weighing 26.7 g. Remnant communicating with main duct estimated at 3.3 g. Followed by transient diabetes gravis. December 4, nerves to remnant broken. December 11, Bernard puncture. December 15, puncture repeated. December 19, acute death from another puncture. Autopsy negative. Pancreas-remnant weighed 13.3 g.

Microscopic Examination of Pancreas Remnant.

The tissue appears fully normal. There is neither fibrous tissue nor œdema to account for the gain in weight; it is all healthy parenchyma. Acinar cells are normal and full of zymogen. Islets are relatively few, as if they had failed to keep pace with the growth of the acinar tissue; but when found they are entirely normal. Transition forms are absent.

The difference between 3.3 g., estimated at operation, and 13.3 g., found at autopsy, represents a remarkable hypertrophy of the remnant in this instance. It can easily explain the cessation of diabetes. The reason for such extreme hypertrophy in a few cases and its relative absence in other cases in unknown. Microscopically, the hypertrophy is found to be genuine; the large remnant consists of normal parenchyma; evidently the greatest increase has been in the acinar tissue, but the islets must have increased to a considerable extent also.

Dog 151.

November 21, removal of pancreatic tissue weighing 31.6 g. Remnant communicating with main duct estimated at 3.2 g. Followed by diabetes levis.

December 4, death under anæsthetic.

Autopsy negative. Pancreas-remnant weighed 11.3 g.

Microscopic Examination of Pancreas Remnant.

The interlobular septa are slightly thickened; otherwise fibrosis is absent. Acini are packed tightly together, and their cells full of zymogen; but there is the impression of an excessive number of nuclei, and apparently of young cells with basophilic cytoplasm crowding in among the mature cells. The islets appear as if hyperplastic and increased in number; many of them are

very small, some narrow and elongated, some large; but all alike are packed tightly with normal, vigorous-looking cells. Mitoses are not seen in either acini or islets. There must have been active hyperplasia to produce the increased size of the remnant, but the active period is over. The islets have not lagged behind the acini. Transition forms are absent.

This is another instance of great and rapid hypertrophy of a pancreas-remnant. Hyperplasia of islet tissue evidently kept pace with that of acinar tissue. Interesting questions are raised. It may rather safely be assumed that the glycosuria would have been transitory; *i.e.*, the case would have been transient diabetes levis if the dog had lived longer. But the fact remains that at this time the dog was heavily glycosuric on bread diet. If 11 g. of the original pancreatic tissue is left in situ, no dog ever shows diabetes levis. The functional status of the new-formed tissue and its numerous islets is therefore open to inquiry.

Dog 159.

December 1, subcutaneous injection of 7 g. dextrose per kilo.

December 11, three Bernard punctures.

December 13, dog weak; same dextrose injection as before. Injection given before 11 a.m.; dog found dead 2 p.m. Autopsy negative.

Liver and pancreas both normal on microscopic examination. Islets normal in all respects.

Dog 172.

December 20, removal of pancreatic tissue weighing 14.4 g. Remnant about main duct estimated at 1.3 g. Duct cut between ligatures. Diabetes gravis remained absent, and the dog's condition was excellent aside from distemper, on account of which he was chloroformed on December 25. Autopsy negative. Pancreas-remnant weighed 2.6 g.

Microscopic Examination of Pancreatic Tissue.

Fibrosis is unimportant. Acini are normal, and mostly full of zymogen. Islets appear hyperplastic; sometimes they are large, but an unusual number of small islets may be seen everywhere. No transition forms.

Dog 173 (see protocol).

December 20, removal of pancreatic tissue weighing 18.9 g. Remnant about main duct estimated at 1.8 g. Duct cut between ligatures. Diabetes levis resulted.

January 10, removal of half the pancreas-remnant. Condition nevertheless gradually improved, till bread could be eaten without glycosuria.

January 25, killed for autopsy. Gross findings negative. Pancreas remnant atrophic; no communication with bowel.

Microscopic Examination.

Heart-muscle. — Normal.
Liver. — Normal.
Spleen. — Normal.
Kidney. — Normal.
Adrenal. — Normal.

Pancreas. — Fibrous changes vary greatly in different sections, but are everywhere considerable. The walled-off areas of parenchyma are mostly well preserved. A large proportion of the acini are approximately normal, and full of zymogen. Other acini are undergoing atrophy and degeneration. Most striking is the excellent preservation of the islets. In places they appear increased in number, because of the shrinking of the acinar tissue. They are full of normal cells normally arranged, with no sign of degeneration. Even close to the edge of the enveloping fibrous tissue they still remain normal, as shown in Fig. 7.

Summary.

In a few instances, islands of Langerhans were not demonstrated in these non-diabetic animals; but the failure was in every instance explainable by disorganization of the tissue or other features mentioned in passing. In general, this series is characterized by good preservation of the islets. It represents a variety of experimental conditions, generally with removal of considerable pancreatic tissue, and sometimes with extensive fibrous or other changes in the pancreas. In every instance where the state of the tissue has permitted distinct recognition of cellular elements, the islets have been found present and their cells normal in appearance. The occasional failure to discover islets, even though they be present, in tissue of this character, is not surprising in view of

the fact that histological investigators, working with normal tissue under the most favorable conditions, have found only one-twentieth of the number of islets which Bensley asserts to be present.

III. Diabetic Dogs.

Dog 185.

January 9, removal of pancreatic tissue weighing 16.9 g. Remnant communicating with main duct estimated at 2 g. Transient diabetes gravis.

January 17, removal of pancreatic tissue weighing 0.7 g. Followed by diabetes gravis, which showed evidence of being transient. On January 26, as the glycosuria was apparently near the point of disappearing, the dog was killed for autopsy. General findings negative. Pancreas remnant apparently healthy; not weighed.

Microscopic Examination.

Heart-muscle. — Normal.
Liver. — Normal.
Spleen. — Normal.
Kidney. — Normal.
Adrenal. — Normal.

Pancreas. — The remnant is buried in adhesions, but very well preserved. Acini are entirely normal, and well filled with zymogen. An unusual number of small ducts are seen everywhere. The islets are nowhere increased in size, but the striking feature is the large number of small (presumably young) islets springing up everywhere through the parenchyma. The appearances suggest a new-formation of islets from ductules. The islet cells appear normal. See Fig. 8.

ligatures. main

Dog 19. emp.

Auto.

February 7, removal of pancreatic tissue weighing 27.8 g. Remnant communicating with lesser duc t estimated at 0.5 g. Diabetes gravis.

pancrea

March 21, removal of about seven-eighths o maf thyroid. April 11, ligatures placed to destroy most of left adrenal onl. April 21, death during laparotomy.

Autopsy negative. Pancreas remnant weighed ay 0.5 g.

Microscopic Examination of Pancreas Remnant. — Considerable scar-tissue present, mostly in the form of coarse bands. Acini are normal, and well filled with secretion. Islets are almost absent. By long search, the possible degenerate remains of two or three of them are found. Here spaces exist, approximately as for a normal islet, but the cells are reduced to three or four in number, and these show advanced degeneration. It is not an invasion by fibrosis or any other agency from outside, but a simple degeneration and disappearance of the islet cells.

Dog 20.

December 7, removal of pancreatic tissue weighing 14.7 g. Remnant communicating with lesser duct estimated at about 3 g. Diabetes gravis.

January 21, removal of left adrenal. February 2, removal of most of right adrenal. Death February 4, from necrosis of adrenal remnant.

Autopsy negative. Pancreas-remnant weighs 2.7 g.

Microscopic Examination of Pancreas-remnant. — Fibrosis is limited to a few large bands of scar-tissue, the gross results of the operation. Acini are entirely normal and the cells full of zymogen. Islets are almost absent. Long search reveals a few small possible ones; it is hard to say with certainty that they are islets; the few existing cells are degenerating and not positively recognizable. Occasional small fibrous areas may represent the former sites of islets; but in general they seem not to be replaced by fibrous tissue, but rather crowded out by the acini pressing on all sides.

Dog 38.

June 30, hepatic artery and nerve-plexus cut between ligatures.

August 2, removal of pancreatic tissue weighing 13.7 g. Remnant communicating with main duct estimated at 2 g. Diabetes levis.

September 14, removal of 0.5 g. pancreatic tissue. Diabetes gravis.

October 7, pancreatic fistula established.

October 13, death from cachexia, with one small abscess near the pancreas remnant.

Autopsy negative.

Microscopic Examination of Pancreatic Tissue.

A. Tissue removed at operation September 14. Parenchyma free from fibrosis. Acini normal, and their cells full of zymogen. Islets few, but not abnormally so. They are of small size, but normal in structure and in the appearance of the cells.

B. Autopsy-remnant. Fibrosis is more evident than before, but is essentially interlobular and leaves parenchyma unharmed. Acini are normal and full of secretion. Small islets are present in normal number, but show advanced diabetic changes; most of the cells are missing; the remaining ones are degenerate and apparently ready to disappear; nuclei are pyknotic; cytoplasm is deficient, leaving sometimes only a naked nucleus.

Fig. 9 shows the typical low-power appearance of islets under these conditions. This area was chosen notwithstanding the accidental patch of stain in the left lower corner, because of the two islets in one field, and also as showing that the occasional thickened septa, like the one in the left lower corner, have nothing to do with the islets.

Dog 49.

May 22, removal of pancreatic tissue weighing 14.8 g. Remnant about main duct estimated at 0.5 g.; another about lesser duct estimated at 0.2 g. Diabetes gravis.

June 3, subcutaneous injection of 12 g. dextrose per kilo. June 4, death from weakness. Autopsy negative.

Microscopic Examination of Pancreas-tissue from About Main Duct. — By far the greater portion is fibrous tissue. The small pancreas-remnant imbedded in the mass is cut up in all directions by fibrous invasion. The acini remain well-preserved and full of zymogen granules. Islets are very scarce, and show the usual loss of cells and degenerative changes in those that remain. No transitions.

Dog 63 (see protocol).

June 13, removal of pancreatic tissue weighing 16.75 g. Remnant communicating with main duct and perhaps with other ducts estimated at 4.7 g. Glycosuria subsequently absent on diet of bread-and-meat mixture.

July 17, Bernard puncture, followed promptly by acetonuria as well as glycosuria; permanent diabetes gravis.

August 4, death from weakness. Autopsy negative except fatty liver. Pancreas remnant weighs 5.55 g.

Microscopic Examination of Pancreas Remnant.

There is moderate inter-acinar fibrosis everywhere, probably a reaction to surgical injury, for it does not destroy either acini or islets. The acini are normal and their cells full of zymogen granules. Islets are present in approximately normal number, but appear as if beginning to degenerate; the process may be an earlier stage of that which is seen in extreme form in dogs which have died after a more prolonged diabetes. The regular arrangement inside the islets is lacking, apparently from loss of some cells; the cells remaining are seldom fully normal, the nuclei are often pyknotic, and the cytoplasm more or less deficient, leaving sometimes a naked nucleus. The change does not result from fibrous invasion. See Fig. 10.

Dog 64.

June 7, removal of pancreatic tissue weighing 22.2 g. Remnant communicating with main duct estimated at 2 g. Diabetes gravis.

August 17, ducts of remnant cut between ligatures.

August 19, found dead.

AUTOPSY.

Bodily appearance is like starvation.

Cause of death is gangrene of duodenum, beginning shortly below pancreas remnant, and due to cutting off blood-supply in operation. Pancreas-remnant is not necrotic; somewhat fibrous, but not diminished in size.

Liver weighs 375 g.; very fatty, and very large compared with the other atrophic organs. Viscera otherwise negative.

Microscopic Examination of Pancreas Remnant. — Considerable scar-tissue is present, and also inter-acinar fibrosis. Acini are of normal appearance, and the cells full of secretion. No positive islets can be found (13 sections). Rare structures containing one or two dying cells might be interpreted as the necrotic remains of islets, but could as easily be called degenerate acini.

Dog 89.

September 17, removal of pancreatic tissue weighing 13.7 g. Remnant communicating with main duct estimated at 1.2 g.; end of processus uncinatus transplanted subcutaneously, also estimated at 1.2 g.

October 4, removal of subcutaneous graft. Weight 3.3 g. Diabetes levis.

October 30, removal of 0.5 g. pancreatic tissue from duodenal remnant. Diabetes gravis.

November 22, duct cut between ligatures.

November 29, found dead of peritonitis. Viscera negative. Pancreas remnant weighed 1.75 g.

Microscopic Examination of Pancreatic Tissue.

A. Subcutaneous graft, removed October 4. Slight fibrosis is present, mostly of interlobular character. A minority of acini are more or less degenerate; the majority are normal and full of zymogen. Islets are present in normal number; they appear small, probably from emptiness of capillaries. A few of them show slight degeneration; the cells of the majority of them are normal in appearance. A few pseudo-islets consisting apparently of decadent acinar cells are also present; in some cases the distinction between true and false islets is difficult or doubtful.

B. Remnant found at autopsy. Postmortem change is present. The entire remnant is extensively fibrosed. Many acini remain normal; many others are in different stages of degeneration. No islets were found (17 sections).

Dog 90.

September 18, removal of pancreatic tissue weighing 16.7 g. Remnant communicating with main duct estimated at 1.4 g. End of processus uncinatus transplanted subcutaneously estimated at 2.4 g. Diabetes gravis.

September 25, death from pneumonia. Autopsy negative. Duodenal pancreas-remnant weighed 1.9 g. Subcutaneous graft weighed 4.2 g.

Microscopic Examination of Pancreatic Tissue.

A. *Subcutaneous Graft.* — Fibrosis is in progress, varying in different portions of the sections, but everywhere is in very early stages. Acini mostly remain normal; a considerable number show degenerative changes. Islets cannot be distinguished with certainty. In some fields, there is an appearance as of large, hypertrophic islets anastomosing with one another by long branches; the cells under low power resemble islet cells, but they are classified by Prof. Mallory as endothelial leukocytes; it is there-

fore an inflammatory process. Degenerating acini also form pseudo-islets. It can be said with certainty that no normal islets are present. Any further decision is made difficult by confusion between degenerate islets, degenerate acini, and endothelial leukocytes. It would appear as though the incipient fibrosis in this gland had attacked the islets selectively, but judgment is difficult for the reasons stated.

B. *Remnant about Duct.* — The tissue in some respects resembles A, but inflammation and connective tissue invasion are much less. The acini are practically normal throughout. Some pseudo-islets exist, but also a considerable number of true islets. Their cells are mostly of fairly normal appearance; there is however a little disorganization, and a deficiency of cytoplasm in some cells. Some islets are also invaded by young connective tissue. The changes might be interpreted as a very early stage of the process which leads to the striking islet-changes seen after prolonged diabetes.

Dog 104 (see protocol).

October 1, removal of pancreatic tissue weighing 21.2 g. Remnant communicating with both ducts estimated as one-fourth of the gland. No diabetes.

October 19, a small wire passed about portal vein, with ends protruding outside abdomen. November 20, the wire slipped out, without having obliterated the vein.

November 27, removal of 6 g. pancreatic tissue from middle portion of remnant, so as to leave two remnants, one communicating with each duct. Diabetes gravis.

December 8, main duct cut between ligatures.

December 21, lesser duct cut between ligatures.

December 23, found dead from gangrene of duodenum. Viscera negative. Combined weight of the two pancreas-remnants was 8.1 g.

Microscopic Examination of Pancreatic Tissue.

A. Tissue removed at operation November 27. Fibrosis is insignificant. Acini are normal and full of zymogen. Islets are comparatively small and scarce, probably not abnormally so. Their cells are normal in arrangement and appearance.

B. *Autopsy Remnant.* — Postmortem change is present. There is much scar-tissue, in the form of enveloping masses and thick septa. Interacinar fibrosis is also present; some acini appear normal; many are in various stages of degeneration. No

islets can be distinguished. Rare trabecular areas may represent the fibrous remains of islets, with one or two cells present, degenerate beyond recognition. A few pseudo-islets also occur, obviously consisting of decadent acinar cells.

Dog 143.

November 9, removal of pancreatic tissue weighing 23.4 g. Remnant communicating with both ducts estimated at 3.7–4 g. Diabetes levis.

November 23, Bernard puncture.

November 29, removal of pancreatic tissue weighing 1.8 g., from middle of remnant, so as to leave two remnants, one communicating with each duct.

December 8, removal of pancreatic tissue weighing 1 g.

December 15, Bernard puncture.

December 21, removal of pancreatic tissue weighing 1.9 g. Duct of smaller pancreas-remnant cut between ligatures. Diabetes gravis.

December 29, main pancreatic duct cut between ligatures.

January 9, starvation begun. January 19, attempted feeding. January 20, found dead. Autopsy negative. Atrophic pancreas remnants together weigh 3.75 g.

Microscopic Examination of Pancreatic Tissue.

A. Tissue removed at operation November 29. Fibrosis insignificant. Acini normal and full of zymogen. Islets entirely normal in number and appearance.

B. Tissue removed at operation December 8. The section contains much scar-tissue, in the form of large masses. Coarse septa cut up the remnant into large areas, but in these the parenchyma is little changed. Narrow strands of fibrous tissue, or a sprinkling of round-cells, may separate acini, but the latter retain normal appearance and activity throughout. Islets are fully normal in number and size, and their cells appear perfectly normal, notwithstanding the occasional presence of a few round-cells.

C. Tissue removed at operation December 21. This fragment happens to contain much less fibrous tissue than B. A few coarse strands are present, but the parenchyma is normal. The acini show the usual richness in zymogen. The islets are normal in number and size, probably not hyperplastic, though a few are unusually large. They are full of normal, vigorous-looking cells.

D. Autopsy remnant. Extensive fibrosis is present; generalized interacinar fibrosis in addition to masses of scar-tissue. The acini are in all conditions, from approximately normal appearance down to extreme degeneration. True islets are apparently absent; rare structures resembling them may be classed as pseudo-islets.

Dog 146.

November 11, removal of pancreatic tissue weighing 22.8 g. Remnant communicating with both ducts estimated at 2.8 g. Diabetes gravis.

December 2, death shortly after a laparotomy. Liver fatty; adrenals small; autopsy otherwise negative. Pancreas remnant weighed 6.3 g.

Microscopic Examination of Pancreas-remnant.

Considerable scar-tissue is present, in the form of large masses. In the parenchyma, fibrous change is slight. Acini everywhere are normal and full of zymogen. Islets are present in normal (or slightly diminished) size and number, but all show a moderate degree of the characteristic diabetic change; viz., diminished number of cells, degenerative changes in those present; cytoplasm diminished, nuclei frequently pyknotic, sometimes naked. See Fig. 11. Apparently, in the presence of such islet-changes, hypertrophy of the pancreas-remnant failed to save this animal from intense diabetes.

Dog 149.

November 16, removal of pancreatic tissue weighing 26.2 g. Remnant communicating with main duct estimated at 1.5 g. Diabetes gravis.

November 20, found dead, cause unknown. Autopsy negative. Pancreas remnant weighs 2.7 g.

Microscopic Examination of Pancreas Remnant.

Postmortem change is present. The parenchyma in general is normal, and the fibrous changes are not marked. Acinar cells are mostly full of zymogen. Exact condition of islets is in doubt because of postmortem changes. If present, they are rare.

Dog 154 (see protocol).

November 24, removal of pancreatic tissue weighing 23 g. Remnant communicating with main duct estimated at 5 g.

December 7, nerves to pancreas remnant broken.

December 15, Bernard puncture.

December 22, removal of 0.95 g. pancreatic tissue. Diabetes gravis.

December 29, pancreatic duct doubly ligated but not cut.

January 31, found dead. Autopsy negative.

Microscopic Examination of Pancreatic Tissue.

A. Tissue removed at operation, December 22. Acini and islets normal in all respects.

B. Autopsy remnant. The fibrous trabeculæ of the gland are thickened, and a moderate inter-acinar fibrosis is present. The acini remain normal, and the cells are full of zymogen granules. Islets are present in about the normal number, but all show the usual diabetic changes, viz., lack of cells, degeneration in the persisting cells, in the form of pyknotic nuclei and disappearing cytoplasm. See Fig. 12.

Dog 155 (see protocol).

November 24, removal of pancreatic tissue weighing 17.7 g. Remnant communicating with main duct estimated at 3.5 g. Diabetes gravis.

December 5, pancreas remnant inclosed in abdominal wall. A portion of the remnant ligated off from communication with the duct.

December 23, pancreatic duct cut between ligatures.

December 25, found dead of peritonitis. Autopsy negative. Pancreas-remnant weighed 6.75 g.

Microscopic Examination of Pancreas Remnant.

There is considerable fibrous tissue, including a general inter-acinar fibrosis. The majority of the acini are normal and their cells full of zymogen granules; but a large number show different stages of degeneration. Islets are very rare or absent; a few may be present, in the last stages of diabetic degeneration. Pseudo-islets are numerous, and the imitation of genuine, slightly altered islets is sometimes rather close. The appearance is particularly confusing in rare instances when the spurious cells are scattered about the fibrous remains of an islet, where a few extremely degenerate islet cells seem to persist. But the spurious cells can be recognized as altered acinar cells by the different stages of tran-

sition which are plainly evident, and by the usual characteristics, viz., size frequently larger than islet cells, cytoplasm and nucleus both dense, opaque, heavy-staining, with generally a basophilic tinge in the cytoplasm. The true islet arrangement is also lacking.

Dog 161.

November 29, removal of pancreatic tissue weighing 11 g. Remnant about main duct estimated at 0.6 g. End of processus uncinatus transplanted under skin, estimated at 1.4 g.

December 12, Bernard puncture.

December 15, Bernard puncture.

December 21, subcutaneous graft subjected to traumatism. December 23, tissue weighing 4.9 g. removed from graft. Diabetes levis.

January 4, pancreatic duct cut between ligatures.

January 17, remainder of subcutaneous graft extirpated; weight 1.15 g. Result was diabetes gravis, which disappeared after 2 or 3 weeks. Toward the end of March, it reappeared as Sandmeyer diabetes.

May 1, killed for autopsy. Gross autopsy negative. Pancreas remnant weighed 2.1 g., chiefly connective tissue.

Microscopic Examination.

Thyroid. — Normal. Colloid moderate in quantity; some follicles empty.

Aorta. — Normal. No fatty or atheromatous changes.

Adrenals. — Beautifully normal. Highly developed gland-like structures in cortex (normal in dogs).

Ovary. — Normal. Numerous ova are seen, some of them approaching maturity.

Pancreatic Tissue.

A. Portion of subcutaneous graft, removed by operation December 23. Fibrosis is slight. Acini are normal and full of zymogen. Islets are normal.

B. Remainder of subcutaneous graft, removed by operation January 17. Fibrosis is more advanced than in A, but the greater part of the parenchyma is well preserved. Acini are still normal in appearance, and the cells are full of zymogen. Islets are small, and appear somewhat compressed; but their cells are normal.

C. Autopsy remnant. The mass consists chiefly of fibrous tissue, containing dilated ducts. There are a few compact areas

of parenchyma, retaining a lobular form; here the interlobular trabeculæ are thickened, but especially, an extreme inter-acinar fibrosis is swallowing up everything. The acinar arrangement is broken up; zymogen is absent; the cells are small, stain poorly, and are undergoing destruction. In some places they form pseudo-islets. True islets are not visible.

Dog 166 (see protocol).

December 12, removal of pancreatic tissue weighing 17.3 g. Remnant communicating with main duct estimated at 5 g. Ligature tied about portal vein so as almost to occlude its lumen, and the ends left protruding outside abdomen. A protruding wire loop also passed about portal vein, but not tied. Diabetes gravis.

December 26, ligature came out, proving vein obliterated.

December 30, found dead from peritonitis, caused by a remaining fragment of wire. Autopsy negative. Pancreas remnant weighed 10.9 g.

Microscopic Examination of Pancreas Remnant.

Postmortem change is present. Fibrosis is moderate. Acini are normal, and their cells full of zymogen. Islets are probably present in approximately normal size and number; there is some question of confusion by pseudo-islets. Postmortem change makes it impossible to decide concerning qualitative changes in the islets. The possibility exists that the present case is one of functional as opposed to organic diabetes.

The hypertrophy of the pancreas-remnant, with diabetes present, is noteworthy.

Dog 167 (see protocol).

December 11, removal of pancreatic tissue weighing 34.4 g. Remnant communicating with main duct estimated at 6.5 g. Untied loops of silk and wire were passed about portal vein, with ends protruding outside abdomen. Diabetes insipidus. December 27, ligatures came out, proving portal vein obliterated.

January 12, removal of pancreatic tissue weighing 2.1 g. Diabetes gravis.

February 20, chloroformed when near death from cachexia. Liver fatty; autopsy otherwise negative.

Microscopic Examination of Pancreatic Tissue.

A. Tissue removed at operation January 12. Normal. Islets entirely normal.

B. Autopsy remnant. Fibrosis is limited to some external scar-tissue, and a slight thickening of some of the natural septa. Acini are normal and well filled with zymogen granules. Islets are present in normal size and number. Some of them are almost normal; others show the characteristic diabetic change in moderate degree; viz., loss of some cells, and occasional other cells with deficient cytoplasm, pyknotic nuclei, or even naked nuclei.

Figs. 13 and 14 show that the islet changes are not as extreme as in typical uncomplicated cases at this stage of the disease. In Fig. 13 the islet in the right upper corner shows noticeably less alteration than the one toward the left lower corner.

In tissue fixed in Zenker fluid without acetic acid, the Bensley stain showed in many of the islets one or two cells full of violet-staining granules (B cells). This is in contrast to all the other diabetic dogs in which the stain was tried, for in them no granules were demonstrable by any method. Whether the difference is significant or accidental must be left undecided. Attempts at fixation in 70 per cent alcohol have yielded uniformly negative results as respects granules.

The impression is conveyed that, as in Dog 166, the diabetes following portal-vein operations is perhaps of more purely functional nature than that following the simple removal of larger fractions of pancreas-tissue.

Dog 171.

December 20, removal of pancreatic tissue weighing 18.6 g. Remnant about main duct estimated at 2.5 g. Duct cut between ligatures. No diabetes.

January 9, removal of pancreatic tissue weighing 2.25 g. Remnant estimated at 0.8 g. Diabetes gravis.

February 17, found dead. Autopsy negative. Pancreas-remnant very small and atrophic.

Microscopic Examination.

Lung. — Normal.

Heart-muscle. — Normal.

Aorta. — Normal. No fat or sclerosis.

Liver. — Congestion. Moderate fatty infiltration.

Spleen. — Normal.

Kidney. — Normal.

Adrenal. — Normal.

Ovary. — Normal. Many normal ova at different stages.

Pancreas. — The mass consists chiefly of scar-tissue, containing a few small areas of parenchyma. These are relatively well preserved. The acini are approximately normal, and mostly well-filled with zymogen. No islets are distinguishable, though rare structures may represent their altered remains.

Dog 176 (see protocol).

December 28, removal of pancreatic tissue weighing 23.6 g. Remnant communicating with main duct estimated at 3.2 g. Diabetes levis.

January 11, removal of pancreatic tissue weighing 0.56 g. January 17, removal of additional tissue weighing 0.6 g. Diabetes gravis.

January 22, pancreatic duct cut between ligatures. February 25, duct found restored, and again divided, this time permanently. For results and discussion, see next chapter.

May 1, killed for autopsy, when weak from diabetes. Gross findings negative. Pancreas atrophied down to a small nodule, chiefly fibrous tissue; no communication with bowel.

Microscopic Examination.

Thyroid. — Normal. Moderate quantity of colloid.

Parathyroid. — Normal.

Adrenal. — Normal.

Testis. — Normal. Active spermatogenesis.

Pancreas. — The mass consists chiefly of scar-tissue containing dilated ducts. In its interior are some small nodules of relatively well preserved parenchyma. Many acini are approximately normal and full of zymogen. Others are broken up or compressed by fibrous tissue and are disappearing by atrophy. Degenerative changes are not prominent, and a return to a poorly differentiated type of cell is rare. Out amid the scar-tissue, scattered clumps, frequently individual acini, are undergoing destruction, but they remain acinar cells to the end; pseudo-islets are absent. True islets are also absent, though in the larger areas of parenchyma, judging by the distinctness of all visible elements, they should be recognizable if present.

Dog 177 (see protocol).

December 28, removal of pancreatic tissue weighing 14.5 g. Remnant communicating with main duct estimated at 1.4 g. Diabetes gravis.

January 6, pancreatic duct cut between ligatures. After rapid cachexia, found dead on January 14. Autopsy negative. Pancreas remnant weighed 2.1 g.

Microscopic Examination.

Liver. — Normal.

Kidney. — Normal.

Adrenal. — Normal.

Pancreas. — Rapidly proliferating connective tissue is spread in thin bands between the acini everywhere. A large proportion of acini retain their normal form and structure, and are full of secretion-granules. A large number also are degenerating and empty of secretion. There is probably some confusion between islets and pseudo-islets, but true islets are present, and apparently little changed. Judgment is difficult, because of appearances like postmortem changes in both acini and islets, which are contradicted by the perfect condition of the nuclei, and by the shot-like distinctness of the zymogen granules with the phosphotungstic stain.

Dog 178 (see protocol).

December 29, removal of pancreatic tissue weighing 20.4 g. Remnant communicating with main duct estimated at 2.2 g. Diabetes gravis.

January 8, pancreatic duct cut between ligatures. February 4–22, starvation, with glycosuria throughout.

April 23, chloroformed for autopsy. Gross findings negative. Pancreas remnant atrophied down to fibrous nodule size of pea.

Microscopic Examination.

Thyroid. — Normal.

Adrenal. — Normal.

Pancreas Remnant. — This is imbedded in dense scar-tissue, containing dilated ducts. Within the parenchyma, fibrosis is surprisingly slight. The acini are perfectly preserved and full of zymogen granules; only a very few are degenerating and seem in some places to form pseudo-islets. Islets are apparently diminished in number. The majority of those present show more or

less of the usual diabetic changes, viz., loss of cells, and degeneration of nucleus and cytoplasm in some of the persisting cells. But numerous islet cells still remain normal in appearance. A few islets also show very little if any distinct abnormality with ordinary stains. Confusion with pseudo-islets is a source of difficulty here. But in general, the islets are much better preserved than in dogs at this stage of diabetes, when the duct has been left patent.

Figs. 15 and 16 show the unusually good preservation of the acinar tissue in this small isolated nodule. In contrast to the acinar tissue, the islets are distinctly altered, but the changes are less than usual in cases where the duct is patent.

Portions of tissue, fixed in 70 per cent alcohol and in Zenker fluid without acetic acid, were stained by the Bensley method. No granules were found in any islet. The stain seemed to be of assistance in distinguishing islet from acinar tissue, since the acinar cells stained, while the cytoplasm of the islet cells remained unstained. Lack of sufficient experience with this method renders it impossible to say whether the absence of granules possesses any significance, or is accidental.

Dog 184 (see protocol).

January 8, removal of pancreatic tissue weighing 22.6 g. Remnant communicating with main duct estimated at 3 g. Diabetes gravis.

January 15, pancreatic duct cut between ligatures.

February 1–20, starvation, with heavy glycosuria throughout.

February 28, chloroformed for autopsy. Liver fatty; other findings negative. Pancreas remnant of almost normal appearance and consistency; weight 4.8 g.; no communication with bowel.

Microscopic Examination of Pancreatic Tissue.

The remnant appears unusually well preserved, for a ligated fragment. The usual fibrosis is present, but is relatively slight, and the sections consist chiefly of fairly normal-appearing parenchyma. The Bensley stain was the only one used in this case. It shows the great majority of the acini well-preserved and normal, but poor in zymogen granules. A few acini are shrunken and atrophic, a few others are degenerating. Islets are rare, small, poor in cells; but yet they seem much better preserved than in diabetic animals at this stage, when the duct has been left patent;

and the changes, when present, are not strictly identical with those in the latter type of animals. No granules are visible in the islet cells with fixation either in 70 per cent alcohol or in Zenker solution without acetic acid; here again, unfamiliarity with the method prohibits any conclusion.

Summary.

Alterations of organs other than the pancreas have not been observed in diabetic animals. In particular, the thyroids, adrenals and sexual glands have been found normal even after prolonged diabetes. The findings agree well with other evidence showing the non-participation of other organs in the diabetic process.

Well-marked changes in the islands of Langerhans have been the predominant feature in the diabetic animals. The observations may be divided into (*a*) miscellaneous findings, and (*b*) typical findings.

(*a*) *Miscellaneous Findings.*

Transient Diabetes. — Dog 185 is the only animal killed at the time when transient diabetes gravis was on the point of disappearing. There was an apparent proliferation of ducts and new-formation of islets. Though the supposition of increase in number is not based on counts through serial sections, the appearances such as shown in Fig. 8 seem to afford sufficient evidence. The question of the functional capacity of such islets was raised in connection with Dog 151 of the non-diabetic series. That animal had a diabetes levis, which (judging by others) would probably soon have disappeared. Numerous "young" islets were also seen in Dog 172. It is possible that these small forms represent recent formations from ducts, in which the cells have not yet attained full differentiation and function; as they ripen and assume function, the diabetes disappears. However, this is speculation, and the number of observations is too few to justify a conclusion.

Functional Diabetes. — In certain instances, the regular procedure has been departed from. For example, in Dog 63, the portion of pancreas removed was not enough to cause diabetes; diabetes was produced by Bernard puncture; yet here the islets showed the characteristic degenerative changes. In Dogs 166 and 167, the portal vein was ligated, in addition to removal of considerable pancreatic tissue. Especially in the former animal,

diabetes occurred with a larger pancreas-remnant than otherwise permits diabetes. The islets did not show such changes as are present in diabetic dogs under "typical" conditions. In Dogs 178 and 184, the pancreatic duct was ligated after the onset of diabetes. The effects of this procedure will be discussed in the next chapter. In these two animals, the islets appeared better preserved than in similar dogs when the duct had been left patent. In all the animals mentioned, the islets showed changes; they could not in any case be called normal. But there is a possibility that in these animals, the diabetes retained more of a functional character than in the cases to be described. At any rate, the visible changes in the islets were less pronounced.

(*b*) *Typical Findings.*

One definite procedure has been followed in the great majority of operations, viz., the removal of nine-tenths (more or less) of the pancreas, leaving the remnant in communication with a duct. As shown in previous chapters, this procedure leads to a regular and definite result, viz., a diabetes which in the earlier stages is relatively mild, but increases with time, till there is apparently a complete inability to utilize dextrose. The microscopic apparently agree with the clinical observations. At the outset the diabetes is apparently in one sense functional; viz., in the sense that the islets show no visible alterations. The only animals killed at a sufficiently early stage were Dogs 177 and 185; but the idea of a functional diabetes at this early stage is confirmed by the fact mentioned in the next chapter, that the diabetes can at the outset be prevented or stopped by suitable methods, whereas it later becomes incurable. At later stages, under the typical conditions, a typical condition of the islets appears to be present in every instance, viz., a visible degenerative change involving all the islets and showing regularly the same picture, viz., loss of cells, deficiency of cytoplasm in many of the persisting cells, degenerating (generally pyknotic) nuclei, occasional naked nuclei. The plates illustrate these changes, which occurred rather early in Dog 49 (a case with unusually small remnants and acute course), and occurred typically in Dogs 38, 63, 146, and 154 (excluding all doubtful cases). With such an advancing degenerative process it would seem inevitable that the islets should finally disappear. Disappearance of positively recognizable islets was noted in Dogs 19, 20, 64, 171 and 176, all being diabetic cases of long standing.

The dogs, and the sections examined from each dog, seem to be too numerous for the result to be called accidental. The acini in these cases were well preserved and the condition of the tissue such as to permit clear recognition of the islets if they were present. In the non-diabetic series, certain animals were excluded because fibrosis, atrophy and other changes made it questionable whether islets could be distinguished if present. Likewise in the present series, all doubtful cases may be placed in a similar list. This list may include Dogs 89, 90, 104, 143, 149, 155 and 161. In some of these cases the histological pictures were fairly clear, and the acinar changes less than in the corresponding non-diabetic list, so that it seemed reasonable to suppose that islets were actually absent. It is not necessary to draw upon any of these doubtful cases in order to complete a diabetic series, which is characterized by gradual degeneration and final disappearance of the islands of Langerhans. In typical cases, aside from accidental changes, the acini have remained normal throughout; in the case of Dog 146, as much as 6.3 g. of normal-appearing acinar tissue was present. In no diabetic animal have the islets remained normal; and in general, the visible changes in them have corresponded to the duration and the severity of the diabetes.

General Conclusions.

These may be (1) concerning transitions; (2) concerning the insular hypothesis.

1. *Concerning Transitions.*

Pictures such as described by Laguesse have been encountered in some cases but could be better interpreted otherwise than as a transformation of acini into islets. They were found especially where atrophic or other alterations in the acinar cells were numerous; in the cases of most active formation of islets (Dog 185, etc.,) they were absent. In some cases a striking power of regeneration of pancreatic tissue has been apparent, in conformity with the results of previous animal investigations, and also of certain clinical observations in diabetes. The numerical relation of islets and acini have indicated that both took part in the regeneration. Laguesse's doctrine of transitions between islets and acini agrees badly with his other doctrine of the specific internal secretory function of the islets; attempts to harmonize the two doctrines

leave them still discordant. The finding of specific islet-lesions in diabetes, without acinar changes, speaks against the interchangeability of the two structures. In the tissues freest from fibrous invasion, post-mortem change or other disturbing factors, transition-forms have been practically absent in diabetes. Under less favorable conditions, the clumps of altered acinar cells resembling islets could generally be distinguished as pseudo-islets. In general, the existing literature indicates a compromise judgment between two opposing views, with a general balance in favor of Laguesse. The weight of evidence tends to confirm the internal secretory function of the islets, the permanent connection of at least a large proportion of islets with the ducts, and the possibility of new-formation of islets in post-embryonic life; but it tends to contradict the one other doctrine of the Laguesse school, viz., of transformations between full-formed acini and islets. The results of the present investigation harmonize with the above interpretation of the former evidence.

2. *Concerning the Insular Hypothesis.*

The findings contribute evidence in favor of this hypothesis. In fact, if they are confirmed, they furnish the particular evidence which has long been sought, viz., specific alterations of the islets with good preservation of the acinar tissue. These alterations seem to result very readily, if investigators will merely refrain from unnecessary complicating procedures in connection with the removal of pancreatic tissue. The effects of duct-ligation are considered in the next chapter. In the series of non-diabetic animals, it was noted that the acinar tissue might be very extensively altered or destroyed, without diabetes. In the series of diabetic animals, large remnants of healthy-appearing acinar tissue were frequently present. The contrast between the two series seems to be found in just one point; in the former series, preservation of islets; in the latter series, degeneration of islets. The clinical contrast between the two series apparently is limited equally sharply to one point; the former animals were able, the latter animals were unable to utilize dextrose. The results are in favor of the hypothesis that the islands of Langerhans furnish the specific internal secretion (amboceptor) which is indispensable for the utilization of dextrose in the body. Under normal conditions, this secretion is presumably furnished chiefly or entirely by the islets, which are a type of cells specialized for this purpose.

The possibility that under abnormal conditions the acinar cells may assume more or less of this function will be discussed in the next chapter.

The results do not necessarily mean that the islands of Langerhans normally furnish the only internal secretion of the pancreas. The above series of dogs, like the occasional animals described by Minkowski and others, seem to be (in later stages, when the islet-changes are maximum) as totally unable to utilize dextrose as totally depancreatized animals. But in other respects they resemble normal dogs and differ from totally depancreatized dogs; viz., the enormous increase of nitrogenous loss is absent, the increased fat-metabolism noted by Falta is apparently absent, the rapid cachexia is generally absent, the absorption of food is generally satisfactory, and the power of wound-healing and resistance to infection is practically normal. The most striking anatomical difference between these dogs and totally depancreatized dogs is the possession by the former of a considerable mass of normal acinar tissue. Therefore the opinions held by Zunz and Mayer, Lombroso and others apparently receive support; and the judgment may again be that there is right on both sides of the question. The pancreas possesses more than one internal function. Concerning the question of the seat of these other functions, there are four possibilities; (*a*) they may reside in the islets alone; (*b*) they may reside in the acini alone; (*c*) they may be shared by the islets and acini; (*d*) they may be shared by the pancreas and other organs. A further bare possibility, viz., that the duct-cells, which may produce both acinar cells and islet cells, may themselves exercise some internal function, is disregarded because of its apparent improbability.

(*a*) If the other internal functions, like the carbohydrate function, are confined chiefly or solely to the islets, it must be maintained that some traces of islet tissue remain even in the most extreme cases, and that these preserve their other internal functions after loss of the carbohydrate function. The view is not probable.

(*b*) If the other internal functions are confined to the acini, some explanation must be found for those cases in human pathology, in which the pancreas has been reported as atrophied to nothing but islets, also the experiments with rabbits, in which it is claimed that nothing remained of the pancreas but islets. However, it is known that islet-tissue sometimes suffices to prevent

glycosuria when it is very hard to discover microscopically, and a similar rule may hold for acinar tissue. It would seem that no case in man or dog presents a positively demonstrated disappearance of even the last degenerate remains of acinar tissue. In rabbits the complete disappearance of acinar tissue may be assumed, since even the ducts were found absent; but in the rabbit other organs perhaps act vicariously.

(*c*) The possibility exists that certain internal functions may be normally or potentially shared by islets and acini. Both structures are produced from the same source, viz., the duct-cells, and may possibly retain some things in common.

(*d*) The possibility that other organs normally or potentially share certain pancreatic functions has been mentioned by authors, to explain the differences between dogs with Sandmeyer diabetes and totally depancreatized dogs. But there is reason to believe that when the sole pancreas-remnant, no matter how old or atrophic, is completely extirpated, the animal becomes in every respect like any other totally depancreatized animal.

We may conclude that possibilities (*a*) and (*d*) are improbable, and that some choice is open between (*b*) and (*c*). The evidence is in favor of some participation of the acini in the internal function of the pancreas, and agrees with the observations to be mentioned, of relations between the internal and external functions of the gland. Lepine's conception of "bipolar" pancreatic cells may therefore still be admissible.

The present study is necessarily incomplete in many respects. It has been necessary to devote more attention to the clinical than to the anatomical side of the question. Owing to limited facilities, the tissues of many animals have remained unstudied. The anatomical results and conclusions await confirmation and extension by those who may devote special research to this side of the question, killing the animals at different intervals after operation, and studying the tissues by means of such methods of fixation and staining as may be indicated. A particularly interesting field for the Bensley or other special differential methods would seem to be offered here.

A closing word may be proper concerning the cause of the changes in the islets in these diabetic dogs. The simplest explanation is that the changes represent over-stimulation and exhaustion. The work of the entire number of islets is thrown upon one-tenth

of them; in the attempt to respond they break down first functionally and then organically. The microscopic picture suggests such exhaustion. Also, in certain early cases, especially when diabetes was about to disappear, pictures of hyperplasia of the islets were found; presumably in these cases the response to the stimulation was successful. It is possible that animals killed at just the right stage of diabetes may regularly show regenerative attempts on the part of the islets.* Other conceivable explanations of the islet changes might attribute them to (1) sugar, (2) inanition, (3) the diabetes itself.

(1) Cat 15 and other animals afford sufficient evidence that islet changes of this nature are not produced by simple excess of circulating dextrose or other sugars.

(2) Animals subjected to starvation and various other influences have shown that neither inanition, nor a combination of it with excess of different sugars, produces these changes in the pancreas.

(3) The suggestion that the islet-changes may be the result instead of the cause of the diabetes is improbable. If admitted, it would still indicate a highly specific relation between the disease and the islets. In some instances, as in connection with duct-ligation or after obliteration of the portal vein, the fully typical changes in the islets have not been present, though the diabetes was intense. Human cases also prove that even severe diabetes may fail to produce these changes in the islets.

Here the other question arises, as to why these pictures of over-stimulation are not found in human diabetes. The difference is probably not one of species; it is a safe prediction that a human patient operated upon in the same manner as these dogs would show a similar diabetes and probably the same islet-changes. The best test of the prediction is to try the operation on monkeys. The suggestion has several times been ventured that men and monkeys may be made diabetic more easily than dogs; that removal of a smaller proportion of the pancreas may produce diabetes. It would not be surprising if removal of $\frac{3}{4}$ $\frac{4}{5}$ of the pancreas should produce diabetes in monkeys; it would not be surprising if men were more susceptible to diabetes than

* This possibility is strengthened by certain findings in diabetic pancreases. Among the degenerating islets in the typical advanced cases, I have regularly observed a noticeable number of small elongated islets, like those pictured in Dog 185, but containing only remains of cells. It is as if there had been first a regenerative attempt and then the cells in the new-formed islets had suffered degeneration like the rest.

monkeys (especially as persons with more highly developed nervous natures are more subject to diabetes than the more animal-like classes). Misconceptions concerning the pancreas may thus be cleared away. It is not true that a tiny fraction of the gland can perform the function of the whole. The pancreas is a very vital and hard-working organ; if it is totally removed, the bodily supply of amboceptor is used up within a very few hours; if nine-tenths of its function is lost in dogs (and presumably smaller fractions in man) a *severe* diabetes results, and correspondingly milder diabetes from correspondingly less impairment of function. Now, operative diabetes in monkeys (or man) would presumably be followed by similar islet changes as in dogs. The hypothesis that these changes represent exhaustion does not complicate the situation; whatever hypothesis is adopted, the fact still remains that operative diabetes is attended by certain islet changes, and the question still remains open why these changes may be absent in the spontaneous disease. Operative diabetes is a simpler, more definitely controllable condition; and here it is feasible to adopt the simple hypothesis that the changes in the islets represent degeneration due to over-stimulation.

The question concerning the clinical disease may then be taken up. In the first place, it must be remembered that anatomical islet-changes do frequently occur in human diabetes; sometimes they are of degenerative character; sometimes the proliferative processes in the islets appear to indicate a strong specific stimulation. Saltykow has considered that in one patient the hyperplasia [as in some dogs] was successful, even to the point of curing the disease. But whether the organic picture is present or not, nothing is better established than the *functional* evidence of over-stimulation of the pancreas in diabetes. Rest of the carbohydrate function strengthens it; over-strain breaks it down. The same rule applies to dogs with diabetes levis. We seem to have here the clear physiological evidence of over-strain of an internal function. It is not probable that this strain affects the pancreas directly — that it is the direct effect of circulating substances upon the pancreatic epithelium. Rather, the pancreatic function is governed from nervous centres, and the stimulation comes through the nerves. Some evidence to this effect is afforded by Dog 63, in which diabetes resulted from the Bernard puncture; the pancreas-remnant was larger than usual, the fatal termination came sooner than usual, yet the islet-changes were well marked. Notwith-

standing the similarity of clinical course, we must still confront the distinction between operative diabetes and the spontaneous disease. The former is essentially organic; there is the organic loss of most of the pancreas; the nerve-centres governing the remnant react vigorously to the needs of the body; the few remaining islets are over-stimulated and break down. In the clinical disease, the organic element must be recognized; but it must also be admitted that at the beginning of most cases and at the end of some cases, there are no visible specific alterations in the pancreas. It is preëminently a functional condition; the islets are present and able to respond, but do not respond because of some failure of their nervous regulation. The recognition of the functional nature of the changes in most cases of human diabetes is the basis of hope for the successful modification or cure of the disease. This subject is to be pursued further in the next chapter.

In concluding this chapter, it is a pleasure once more to state that the whole of it was made possible solely by the coöperation of Dr. F. B. Mallory. The entire work of preparing the sections was performed by him. Including pancreas and other organs, this work covered several hundred different specimens, with two or more different stains for every specimen, and several sections prepared with each stain, amounting in all to several thousand sections. Many of the more important details, including various experiments concerning staining methods, were carried out by him personally. To his skill are due the beautiful histological preparations obtained, which have facilitated the study of the various confusing points. This study was also conducted under his direction, and in all doubtful questions I have been guided by his advice. Only the conclusions, especially the relation of the tissue-changes to diabetes, have been my independent responsibility; and if they are incorrect, Dr. Mallory is in no way involved in the error. My sincere thanks are here expressed to Dr. Mallory, not only for the invaluable aid, but also for the characteristic spirit of kindness in which it was given.

CHAPTER XXII.

RELATIONS OF INTERNAL AND EXTERNAL PANCREATIC SECRETION.

AMONG the subjects treated in the preceding chapter were the anatomical effects of ligation of the pancreatic ducts. The present chapter will be concerned with the functional results of this procedure. The subject will be divided into: 1. The absorptive function; 2. The carbohydrate function.

1. The Absorptive Function.

This question concerns the rôle of the pancreas in the absorption of food. An exhaustive review of the literature will not be attempted, but the works to be considered will be divided into A. Experimental, and B. Clinical.

A. EXPERIMENTAL.

The earliest literature of the subject is reviewed by Abelmann and others. Claude Bernard obtained temporary closure of the pancreatic ducts in two dogs by the method of oil-injection, and during the period of this closure the animals showed fatty diarrhea. It was also observed that in rabbits, in which the pancreatic duct enters the intestine 30 or 35 cm. below the bile-duct, the lymphatics from the portion of bowel above the pancreatic duct show no absorption of fat, although those from the portion below the pancreatic duct are white with fat. Dastre [ref. in texts] by surgical means caused the bile to enter the intestine $\frac{1}{2}$–$1\frac{1}{2}$ metres lower down, and then found that no absorption of fat occurred above the bile-opening. One theory therefore has been that both bile and pancreatic juice are necessary for the digestion and absorption of fat.

Abelmann, in Minkowski's laboratory, found that depancreatized dogs absorb on an average 44 per cent of food-protein, and dogs with pancreatic remnants not communicating with the bowel an average of 54 per cent. Feeding of fresh pancreas raised

the protein-absorption to 74–78 per cent. Carbohydrate absorption is better, but yet 20–40 per cent of starch is lost. After total pancreatectomy, all fat fed is excreted in the feces; but pancreas feeding produced a considerable absorption of fat; the best instance was one in which the diet was 500 g. meat, 120 g. pancreas, and 30 g. butter, containing 77.8 g. fat and 24 g. nitrogen; of the fat only 21.05 g. was excreted, and of the nitrogen only 5.25 g. was excreted in the feces. The bile was apparently normal. Even in totally depancreatized animals without pancreas feeding the fats were largely split; the portion split varied from 30 to 85 per cent, depending upon the quantity ingested and the duration of its sojourn in the bowel. The fatty acids were excreted chiefly in the form of soaps. Artificial emulsions of fat, except when made with pancreas, were utilized no better than plain fat, but in the form of milk there was always some fat-absorption, from 30 to 53 per cent, depending upon the quantity ingested. Dogs with partial extirpation of the pancreas and exclusion of all pancreatic juice from the bowel absorbed better than totally depancreatized dogs; small quantities of non-emulsified fat were absorbed to the extent of about half; with larger quantities the absorption was not below 31.5 per cent; and up to 80 per cent of milk-fat was absorbed. Abelmann suggested that the difference between totally and partially depancreatized dogs is due to a transport of ferments from the pancreatic remnant by the blood, and their excretion into the bowel by other glands.

Sandmeyer performed extensive metabolism experiments on dogs diabetic after partial pancreatectomy and subsequent atrophy of the remnant. He found proteins to be absorbed to the extent of 62–70 per cent. The utilization of non-emulsified fat varied widely; sometimes zero, sometimes 30 per cent, up as high as 78 per cent. Milk-fat was absorbed up to 42 per cent. Pancreas feeding improved considerably the absorption of both protein and fat.

Harley reported that in dogs, free from diabetes after removal of most of the pancreas, the absorption amounted to little more than 17.8 per cent of the nitrogen of the food; and of the fat, the absorption was 26–38 per cent while the general strength was good, and only 4.44 per cent after the animal had become weak. A normal dog fed on milk was found to absorb 21–46 per cent in 7 hours; but after total pancreatectomy, none of the fat was absorbed within this time.

Hedon and Ville found that after total pancreatectomy (performed in two stages), a dog is able to absorb approximately 18 per cent of lard or oil. After biliary fistula, it can absorb about 69 per cent of milk-fat and about 45 per cent of olive-oil. After biliary fistula and incomplete pancreatectomy (excluding all pancreatic juice), absorption was greatly reduced, but was still present to the extent of 22 per cent of milk-fat and 10 per cent non-emulsified fat. In all cases the splitting of fat was efficient; the fecal fat was chiefly in the form of free acids, and these made up as high as 90 per cent of the total. Hedon (4 *A*) studied the question further by means of examination of the chyle. After total extirpation of the pancreas (in two stages) the lymph of the thoracic duct was white with fat after lard-feeding. The same was found after biliary fistula. With a combination of biliary fistula and total pancreatectomy, the lymph was faintly opalescent after lard-feeding, indicating a very slight absorption of fat.

Levin also used the method of examining the lacteals. In some dogs the pancreas was extirpated, in others the portion of the duodenum receiving the bile and pancreatic ducts was isolated, and in others a biliary fistula was produced. All were fed with cream and killed 5 hours thereafter. The lacteals and the cells of the villi were empty of fat. The author concludes that the simultaneous action of bile and pancreatic juice is necessary for the normal absorption of fat, though without them some fat can still be absorbed as soap.

Cunningham ligated the bile-duct, and either ligated the pancreatic ducts or extirpated about half the pancreas. The fasting dogs were then given milk, emulsified oil, or pure codliver or cottonseed oil, and were killed 6–20 hours thereafter. It was thus found that the absorption of fat was merely delayed, not prevented; for after a sufficient number of hours the lacteals were white with fat. It was also shown that neutral cottonseed oil can be absorbed by a well-washed loop of intestine arranged as a Vella's fistula.

Rosenberg worked with non-diabetic dogs, without removal of pancreatic tissue, but with the organ carefully separated from the intestine and usually atrophied in extreme degree. Under these conditions the absorption of fat, protein and carbohydrate was good, often standing above 90 per cent. After not quite complete extirpation of the pancreas-remnant, the absorption dropped to about half the former figure, but rose markedly when

pancreas was fed. Under all conditions, the fat lost in the feces consisted chiefly of free fatty acids, not neutral fat. The author interprets the findings as indicating that the presence of the pancreas, even when isolated from the bowel, is of influence in the absorption of food, probably by reason of a transport of ferments through the blood. He explains the conflicting results of other authors as due to initial removal of a large proportion of the pancreas, peritonitis, and other complications.

Pende (1) reported that digestion of fat and albumin is undisturbed after ligation of the pancreatic ducts. The zymogen granules disappear from the pancreas in 1 or 2 months; the reaction to pilocarpin disappears in about a week. The saliva, bile, and the organs secreting them are unchanged.

Happel found absorption impaired by ligation of the ducts. In one of his dogs the loss of fat in the feces amounted to 95.27 per cent.

Lombroso's findings, to be mentioned later, were attacked by several authors. Burckhardt claimed that an isolated portion of pancreas is without influence upon the absorption of food, unless there is an open fistula which is licked by the dog. When the fistula is closed or the dog prevented from licking it, the absorption promptly falls to a low figure. The influence of the pancreas upon alimentary processes is therefore solely through its external secretion.

Hess and his pupil Sinn contended that Lombroso had not ligated all the pancreatic ducts, and that this error accounted for the failure of pancreatic atrophy and the excellent absorption of food reported by him. In Sinn's dissertation, normal absorption is reported in most of the dogs, because certain ducts were not ligated. In two animals the ligation was successful, and the entire pancreas underwent sclerosis. In one of these the absorption of nitrogen was 42 per cent, of fat 48.4 per cent; in the other the absorption of nitrogen was 78.7 per cent, of fat 89.9 per cent. A considerable difference is here evident, even when the ligation was perfect and the entire pancreas sclerotic.

Lombroso's publications on this subject are numerous (see 1, 2, 4, 5, 7, 8, 9, 11, 13). After complete separation of the pancreas from the bowel, he has found almost normal utilization of food-substances. When the entire pancreas was extirpated except a subcutaneous graft, absorption was not so good; from 25 per cent to over 50 per cent of the food-fat appeared in the feces. The

dogs, in spite of good digestion and absorption, often died of marasmus. The pancreas generally was well preserved, but sometimes a rapid atrophy occurred. The atrophic changes either in the whole pancreas, or in a subcutaneous graft, were considered by Lombroso responsible for the impaired digestion which accompanied them; whenever the pancreas was well preserved the absorption was good. The influence of the pancreatic remnant upon absorption was shown to be independent of the animal's licking the fistula. After total extirpation of the pancreas — irrespective whether performed at once, or whether the ducts were first ligated and the gland removed some time later, or whether all was extirpated except a subcutaneous graft which was removed later — the animals regularly excreted not the same, but a greater quantity of fat than was fed to them. By feeding a pure fat, or pure oleic acid, the author showed that the melting-point of the excreted was different from that of the ingested fat, the relations indicating that a portion of the food-fat was absorbed, and a greater quantity of body-fat excreted. This, and the fatty infiltration of various organs, and other facts, are interpreted to mean that the pancreas plays a part in fat metabolism, and after pancreatectomy fat becomes to a large extent a useless foreign body. Sections of the intestinal mucosa stained for fat showed the droplets present in the cells in large numbers; this was interpreted as representing both absorption and excretion. Feeding of pancreas, or introduction of pancreatic juice directly into the duodenum, changed the absorption very little. The behavior of proteins and carbohydrates was analogous to that of fats. To rule out vicarious action of other glands, the diastatic power was chosen as a test; and it was shown that after ligation of the pancreatic ducts there is no increase of diastatic power in the saliva, gastric juice, bile, or intestinal secretion, and no diminution of this power in these secretions after total pancreatectomy. The enzymatic power of the isolated pancreas was found to correspond to its anatomical condition; when structure was preserved ferments were preserved; when structure was lost ferments were lost. Lombroso's general conclusion is that the pancreas influences intestinal absorption not only through its external but also through its internal secretion.

Zunz and Mayer [see also Zunz (1)] published results in harmony with those of Lombroso. The dogs lived in good condition, and the initial loss of weight was regained. The atrophy of the

pancreas-remnant was of varying degree; in some cases the tissue was preserved for long periods; in other cases the sclerosis was more marked; but the islets were relatively well preserved, and diabetes never occurred till after extirpation of the atrophic remnant; then it appeared in full intensity. The structure of the liver, spleen and thyroid remained normal. For some time after ligature, pancreatic juice was still secreted under the influence of food or secretin. Erepsin, enterokinase and secretin were still present in the intestine several months after operation. The bile acquired no proteolytic power. Absorption of food was good as long as the atrophic pancreas was present, but its extirpation resulted in poor absorption. The authors consider the pancreas indispensable as respects internal but not as respects external secretion. In addition to the internal secretion which prevents diabetes, they believe in the existence of another internal function of the pancreas, in which the acini probably participate.

Fleckseder (2) removed the pancreas except a subcutaneous graft. The absorption was approximately 75–80 per cent N and 60–80 per cent fat. Licking of the fistula, drainage, or stasis were without influence upon absorption. The dogs lost weight and died of marasmus, sometimes with diabetes toward the end. One animal developed intense diabetes after advanced atrophy of the graft, yet the absorption here was approximately 90 per cent of both fat and protein. The author concludes that intestinal absorption is dependent upon the internal secretion of the pancreas; that the external function can be easily replaced; and that the internal function may be gradually replaced also, since there may be good absorption with intense diabetes of the Sandmeyer type.

Niemann experimented with several dogs in which Brugsch had ligated the pancreatic ducts. The absorption of both nitrogen and fat was high, generally near or above 90 per cent. The author concludes that absence of pancreatic juice causes no disturbance of absorption. The pancreas in each case atrophied very rapidly; the dogs were killed 1 or 2 months after operation, and almost total degeneration and sclerosis of the acini was found, with islets well preserved. Trypsin was proved absent from the intestine.

Brugsch (2) likewise concluded that exclusion of pancreatic juice causes no departure from the normal with respect to intestinal motility and absorption. Trypsin was proved absent from

the intestine; also a transportation in the blood was excluded by tests which showed trypsin absent and anti-tryptic power present. When the ducts and vessels of the pancreas were ligated in one experiment, the pancreas rapidly degenerated and absorption amounted to only 39.6 per cent fat and 62 per cent nitrogen; complete atrophy therefore, like extirpation, causes grave digestive disturbance. The steatorrhea and other disturbances sometimes associated with clinical pancreatic obstruction are attributed not to the absence of pancreatic juice but to some associated intestinal disorder.

Visentini (4) differs from the above authors, in finding that after ligature of the pancreatic ducts in the dog, between 60 and 80 per cent of the ingested fat is lost in the feces; and of this quantity, the neutral fat is almost always more than the fatty acids. Exclusion of pancreatic juice is therefore considered to be attended with serious disturbance of both digestion and absorption.

Pratt, Lamson and Marks found serious disturbances of absorption when pancreatic juice was completely excluded from the intestine. The absorption of nitrogen ranged from 22 to 62 per cent, and of fat from 4 to 76 per cent, lower figures being more frequent than high. Feeding of pancreas preparations markedly increased absorption The pancreas remnants showed extreme atrophy.

Jansen performed feeding experiments on one dog, first after extirpation of all the pancreas except a subcutaneous graft, then after removal of the graft. Before removal of the graft, the excreted fat was about 25 per cent of that ingested. After removal of the graft, the excreted fat greatly increased, but was variable. On some occasions it considerably exceeded the ingested fat, but it was deemed questionable whether the excess represented body-fat or delayed fat from the food.

The above results apply to dogs. It may be noted in passing that ligation of the pancreatic ducts in birds gives rise to fatal nutritive disturbance, and in rabbits is without any perceptible effect upon the health or digestion.

B. Clinical.

The fact is well known that absence of pancreatic juice from the bowel is often attended with marked disturbance of digestion and absorption, especially steatorrhea. It would be superfluous

to review most of the literature in this connection, and in what is given, the exceptions will receive somewhat disproportionate prominence.

Litten, Hartsen, and Friedrich Müller described cases of complete absence of pancreatic juice from the bowel, without fatty stools. Müller in particular considered that steatorrhea is due more to associated conditions, especially biliary obstruction, than to the mere lack of pancreatic juice.

Vaughan Harley reported the case of a boy who developed symptoms of pancreatic obstruction after scarlet fever. On milk diet, the feces contained 40 per cent of the ingested nitrogen and 73 per cent of the ingested fat. The excreted fat consisted chiefly of free acids and of soaps. Harley also reckoned that a disorder of metabolism was present, because of loss of weight at a time when the absorbed food was theoretically sufficient for normal nutrition. Pancreas feeding improved the absorption during the brief time it was continued.

Deucher reported metabolism experiments on two men with complete closure of the pancreatic duct, and in one with doubtful closure. The case of doubtful closure showed good absorption (98.3 per cent N, 80.6 per cent fat). In one case of complete closure, the absorption was poor (70.4 per cent N, 17.1 per cent fat); but this was a case of carcinoma with secondary atrophy of the pancreas. The other case, with complete closure and cholecystenterostomy, was intermediate (81 per cent N, 47.4 per cent fat). Fats were split in all cases to the extent of 60–80 per cent; there was little soap except in the case of incomplete closure.

Hirschfeld described a form of diabetes in which, along with glycosuria, there is marked reduction of food-absorption (excretion of 30–45 per cent N and 29.4–47.2 per cent fat). Schild and Masuyama found fresh pancreas generally better than artificial preparations. In one diabetic the expressed juice of the pancreas increased the splitting of fat but not to any important degree its absorption, while the feeding of pancreas in substance almost doubled the fat-assimilation. Salomon has reported improvement of pancreatic steatorrhea from the use of pancreon; two cases showed no improvement, and in these an intestinal disorder was assumed as the cause. E. Meyer (2) reported decided benefit from the feeding of pancreon in a case of pancreatic carcinoma with diabetes. In the three cases of extirpation of most of the pancreas, reported by Franke, steatorrhea was absent.

Keuthe described a patient with symptoms of intermittent diarrhea, weakness and emaciation, and slight alimentary glycosuria after tests. Only 9.8 per cent of the fat of the Schmidt test-diet appeared in the feces, and of this, 92 per cent was split. Death occurred from pulmonary tuberculosis, and the autopsy showed almost complete atrophy of the pancreas, with total obliteration of the ducts, due to stones. In the better preserved portions were numerous hypertrophic islands of Langerhans.

Falta (7) reported cases of clinical hyperthyroidism with fatty diarrhea, which cleared up under X-ray treatment of the thyroid. There is nothing clearly indicating whether the pancreas or intestine was at fault. Bittorf found evidence of an associated organic pancreatic disease under similar circumstances.

Gigon (1*A*) studied the metabolism of a patient with diabetes and symptoms of organic pancreatic disease. The latter began very suddenly, and were interpreted as due to the sudden blocking of the pancreatic duct by a stone. The author considers therefore that the sudden diminution in the absorption can be attributed positively to the exclusion of pancreatic juice; Brugsch (2) holds a somewhat different opinion. The impairment of absorption was not great; on an average about 80 per cent nitrogen and 75 per cent fat were absorbed. Pancreon was given for some time, but after an initial transient improvement, it lost all effect.

Ehrmann (2) reported careful metabolic analyses in a patient with diagnosis of complete pancreatic obstruction due to chronic pancreatitis. The N-absorption was 57.21 per cent without pancreatin, 83.03 per cent with pancreatin. The fat absorption was 49.84 per cent without pancreatin, 72.81 per cent with pancreatin. The splitting of fat, and also the proportion of soaps, was below normal, but improved by pancreatin. Ehrmann's paper also contains additional references to the literature.

Naunyn (p. 280) describes the case of a diabetic girl, with diarrhea and impaired absorption, in whom the pancreas appeared fully normal at autopsy. Similar reports exist in the literature.

Remarks.

All writers are agreed that the evidence is contradictory and confusing. Two minor points are probably easy to clear up. One is the notion that cancer-cells may assume the internal function of the pancreas. There is no evidence in favor of this assumption; from the standpoint of diabetes it conflicts with the insular

hypothesis (since the cancer is not composed of islet cells), and from the standpoint of digestion it is opposed by the following facts: (1) a patient with extreme simple atrophy of the pancreas may digest and absorb as well as one whose pancreas is replaced by a large carcinoma; (2) Franke found that removal of practically the entire carcinomatous pancreas was without perceptible effect upon the assimilation; Brugsch asserts that extensive carcinomatous invasion of the pancreas is a cause of mal-assimilation. An idea more frequently suggested is that the body gradually adapts itself to a sufficiently slow destruction of the pancreas. This suggestion is contrary to observations recorded in the literature. The longest experiments on record are those of Sandmeyer and of Zunz and Mayer. In one of Sandmeyer's dogs, thirteen months were required before the atrophy of the pancreas-remnant was sufficiently advanced for diabetes to begin; but in this as in his other experiments the diabetes always began when the proper stage of atrophy was reached, and progressively increased to an extreme and fatal degree. Zunz and Mayer's dogs carried small, more or less atrophic pancreas-remnants for months without diabetes, yet, when these remnants were removed, the typical diabetes of total pancreatectomy appeared in its full intensity. All accurate findings from the time of Minkowski to the present are in accord with these results. Occasional contrary statements are based either upon (1) apparently complete atrophy of the pancreas, when in fact a certain number of functionating pancreatic cells must have been present; or (2) supposedly complete removal of an atrophic pancreas remnant, not followed by full typical diabetes because the extirpation was not actually complete, the incompleteness being due to the difficulty of finding and removing the whole of an atrophic pancreas. Just as for the anti-diabetic function of the pancreas, so also for its absorptive function, the evidence is against any adaptation to the loss of the gland. The absorptive power of dogs of the Sandmeyer type becomes poor toward the end; they can still absorb to some extent, but so can even a totally depancreatized dog, when conditions are favorable, especially when the operation is performed in two stages. A dog with an extremely atrophic pancreatic remnant generally has a higher absorptive power than a totally depancreatized dog, but when this remnant, however atrophic, is removed, the absorption becomes the same as that of any other depancreatized dog, provided the pancreatectomy is complete.

My experience has been as follows. A small fragment of the pancreas secreting into the bowel has not discharged perfectly the function of the whole. Metabolism experiments [some mentioned in Chapter VI] have shown nitrogen absorption always slightly below that of a normal dog, and the absorption was poorer in case of a very small remnant (as in Dog 19, remnant 0.5 g.) than in case of remnants weighing several grams. There is also some variation independent of the size of the pancreas-remnant and of any obstruction or other complications discoverable at autopsy; though adhesions may be a factor worth considering in regard to some of the different findings in the literature. No analyses concerning fat absorption have been made; gross appearances indicated that the impairment was greater than that of protein, and was greater in the case of Dog 19 than in those with larger remnants. Whenever the pancreatic duct has been ligated, a great change has been evident in every instance. Autopsy has always confirmed the complete separation from the bowel; my experience does not agree with that of authors who have found this a difficult or doubtful procedure. No accurate determinations of absorption were undertaken, but clinical observations always indicated a marked deficiency. Variations existed here also. Some dogs have been able to nourish themselves by eating two or three times as much as normal; the feces were exceedingly bulky but homogeneous. Other dogs have emaciated irrespective how much they might eat, and meat-fragments have been recognizable with the naked eye in the undigested feces. In general, these differences have seemed to correspond somewhat to the state of the pancreas remnant; with the better preserved remnants the dogs have thriven better. Prompt improvement has always followed the feeding of pancreas; the dogs gain weight promptly and require less food. But even if a dog is fed on pure pancreas, the feces have never looked like those of a normal dog or of a partially depancreatized dog with patent duct; they tend to be softer, bulkier and lighter colored than those of a normal dog on the same diet.

These incidental observations therefore are wholly in accord with the view that the pancreatic juice is indispensable for the normal utilization of food, and such is the impression naturally gained from them. But there is no desire to question the observations of others. It is unknown why pancreas-remnants sometimes atrophy more rapidly than at other times. It is not known why

different dogs after the same operation, whether ducts are ligated or not, differ in their powers of assimilation. Individual differences or operative differences perhaps may explain. In so many disputes concerning the pancreas and diabetes, it turns out that both sides are correct, and such may prove to be the case concerning absorption of food after exclusion of pancreatic juice. Positive findings of utilization, if correct, necessarily outweigh negative. It must be concluded either that a considerable number of competent clinical and experimental investigators were mistaken, and that pancreatic juice was not entirely excluded when they considered it to be so, or else the following two facts stand established: (*a*) the external secretion of the pancreas is not essential to absorption; satisfactory absorption is possible in its absence in man and animals: (*b*) deficient absorption is frequently improved by pancreas feeding. Opposing findings are possibly explainable by intestinal disorders, general weakness, and (perhaps most important) injuries of intestinal nerves. If the above positive findings are correct, two possible hypotheses may be advanced to explain them.

1. It may be supposed that the pancreas influences absorption only through its external secretion. Under favorable conditions, the absence of this secretion may be compensated for; but the lack of this powerful digestive juice predisposes to intestinal catarrh and other abnormal conditions, with the result that steatorrhea and azotorrhea frequently occur. In many cases pancreas feeding benefits these conditions, because the valuable pancreatic enzymes are thus restored, digestion is made easier, and the irritation and weakened function of the intestine and other organs are improved. Absorption is poorer after total than after partial pancreatectomy, merely because of the intensity of the diabetes and the impaired function of all organs which it involves. Fatty stools in clinical diabetes are explained by disturbance of the external pancreatic secretion, or of the intestine, liver (bile), or other organs.

2. It may on the contrary be supposed that the pancreas influences absorption through a specific internal secretion. The differences between absorption after total and after partial pancreatectomy are thus explained by the absence of this internal secretion. Disturbances of absorption in clinical diabetes may be due to disturbance of this internal secretion; there may also be impaired absorption (steatorrhea) of pancreatic origin without

glycosuria. The benefits of pancreas feeding may to some extent be explained on the same basis as before, viz., the improvement of local conditions; but perhaps to a greater extent may be explained as a true opotherapy, *i.e.*, the substitution of the internal function of an organ by feeding its substance or extract. This internal function may be performed or at least shared by the acini.

Neither of these hypotheses can be considered as fully established, and probably neither can be accepted in extreme form. The first gives suitable consideration to the external function of the pancreas, which, if not indispensable, is yet highly important. The second probably goes too far in attributing to the pancreas a special function governing absorption, but is correct in assuming that the pancreas has several internal functions, some of which may perhaps be performed by the acinar cells. The following considerations pertain.

(*a*) As noted in previous chapters, these different functions may be experimentally *separated*. Minkowski (6) and Allard (3) have described dogs with pancreatic grafts excreting through the abdominal skin, with total or nearly total diabetes from the carbohydrate standpoint, but without the other symptoms which characterize the diabetes following total pancreatectomy. After total pancreatectomy, wounds heal badly, infection is not resisted, all bodily functions are at low ebb, and the maximum duration of life is two or three weeks. But the other animals described, with the same maximum glycosuria and D/N ratio, may live for long periods with little impairment of any of the other functions mentioned. It was also previously noted that under some conditions azoturia is obtainable without glycosuria. Intense marasmus of pancreatic origin, equal to that of diabetes but without glycosuria, is also obtainable under suitable conditions. These facts indicate the existence of a variety of internal functions of the pancreas.

(*b*) Fleckseder proved that a similar separation is possible between the absorptive and the anti-diabetic functions. One of his dogs with an atrophied subcutaneous graft showed the D/N ratio characteristic of total diabetes, yet absorbed approximately 90 per cent of both N and fat. Fleckseder wrongly interpreted this as an accommodation of the body to the loss of the pancreas. Though such a graft appears so atrophic, yet it enables the dog to live, absorb food, resist infection, etc., whereas its removal at any stage reduces the animal to the same condition as any other

totally depancreatized animal. My dogs have furnished a still different combination, for they have had intense diabetes, along with preservation of a considerable pancreatic remnant and the presence of the secretion of this remnant in the intestine; they have digested and thrived except for the loss of sugar; *i.e.*, the external pancreatic function was preserved in considerable degree, and the internal function was preserved with the single exception of the power of utilization of dextrose.

(*c*) It is not justifiable to assume that the pancreas has a specific regulating function as respects absorption. There seems to be good evidence that a certain degree of absorption is possible even after total extirpation of the pancreas. There is therefore no such total paralysis of this function as Lombroso has claimed. Not only absorption but also motility of the digestive tract suffers after total pancreatectomy; and it is just as unreasonable to assume a specific influence of the pancreas upon absorption as to assume such a specific influence upon motility. It is sufficient to understand that the pancreas exercises several metabolic functions, pertaining to carbohydrates, fats, and proteins; these functions probably consist in supplying amboceptors for the substances in question, and are indispensable for normal anabolism, cell-nutrition, and the general well-being. The total removal of the pancreas then causes impairment of absorption, just as it causes impairment of intestinal motility and impairment of all the functions of all the cells of the body; there is no reason to assume a separate specific influence of the pancreas upon each of these different functions.

Clinical progress will be assisted by the recognition of these different internal functions of the pancreas, and the fact that they may be disturbed together or separately. Harley's patient was free from glycosuria, but had steatorrhea and supposedly also a disturbance of metabolism. Generally the carbohydrate function is preëminently what is disturbed in human diabetes, but the rarer cases may show signs indicative of disorder of other pancreatic functions.

The idea that the benefits of pancreas feeding consist in supplying an internal as well as the external secretion of the pancreas is more purely hypothetical, and has as yet no assured basis. But the facts may be looked at as follows. Certain diabetic or non-diabetic patients and animals have steatorrhea which disappears on pancreas feeding. Other patients and animals appar-

ently furnish the demonstration that the impaired absorption is not due merely to absence of the external pancreatic secretion, for they absorb well when it is totally excluded. Also, the patients and animals with steatorrhea generally split their fat; why therefore do they not absorb it? We can understand how pancreatic juice should aid digestion, but how does it influence absorption? If the benefit consists in improving local conditions, diminishing fermentation, putrefaction, intestinal irritation, etc., it is difficult to see how the changes can be so abrupt; the giving of pancreas is followed by immediate improvement, its withdrawal is followed by immediate relapse. On the other hand, it is possible to suppose that pancreas feeding is without effect upon intestinal, biliary or other local conditions, and that some cases resist pancreas-therapy because they are due to intestinal, biliary or other non-pancreatic conditions. In the cases where pancreas therapy is successful, its effects are so prompt and striking as to justify the belief that they are specific. And since it is difficult to maintain that these effects are due solely to the external pancreatic secretion, and since the possibility of supplying an internal function by the feeding method is established for the thyroid, there is some warrant for the suggestion that some portion of the internal function of the pancreas may be substituted by pancreas-feeding.

2. The Carbohydrate Function.

The evidence concerning the consequences of closure of the pancreatic ducts will again be considered under the headings of A. Experimental, and B. Clinical.

A. Experimental.

It is well known that very small remnants of pancreatic tissue sometimes suffice to prevent diabetes. Sauerbeck (p. 588) states that v. Mering and Minkowski, supported by all German and French authors, have found that diabetes fails to occur if $\frac{1}{6}$–$\frac{1}{12}$ of the pancreas is left. Sandmeyer (2) in two dogs left a portion of pancreas 3 cm. long; in the larger animal diabetes was postponed for 2 months, in the smaller animal for 13 months. Thiroloix repeatedly performed pancreas-extirpations which were called "total," without obtaining diabetes. His pupils Lesne and Dreyfus reported "total" pancreatectomy on 19 dogs, only 11 of which

showed glycosuria continuing till death. De Renzi and Reale claimed that total extirpation of the pancreas does not always cause diabetes. Pflüger (16) refers to the fact that Küttner and Lüthje performed supposedly complete extirpations of the pancreas followed by only transient glycosuria, and slight operative errors were found responsible; also that Capparelli published alleged "complete" extirpations, from which the animals recovered. Vaughan Harley left only one-twentieth of the pancreas, and there was no glycosuria. Burkhardt described a dog in which the pancreas was completely extirpated by Minkowski, except a small subcutaneous graft, and there was no diabetes even after $\frac{3}{4}$ year. Seo (1) worked with dogs depancreatized except for a small subcutaneous graft, sometimes estimated as "about 2 cm. long" and sometimes as "about one-tenth of the gland." The glycosuria following such an operation generally cleared up within a day or two; subsequently, carbohydrate feeding sometimes produced glycosuria, sometimes not. After atrophy of the remnant a diabetes of the Sandmeyer type ensued. On the other hand, Minkowski (6), Allard (3), de Renzi and Reale (1), and others, have reported the occurrence of intense diabetes when a healthy-appearing pancreas-remnant of very considerable size was present in the body. Because of these irregular and apparently conflicting results, considerable confusion has arisen regarding diabetes, and the opinion is generally held that a tiny fragment of pancreatic tissue may be able to prevent diabetes. For this reason, it has been a cause of wonder that diabetes may occur clinically when the pancreas is apparently so little altered; and from this cause again, doubt has been cast upon the pancreatic origin of human diabetes.

Opposed to all these uncertain and discrepant results, I have shown in previous chapters that severe diabetes regularly results when the pancreas remnant represents one-tenth of the gland, and frequently when it is larger. Moreover, Minkowski [(1), p. 27] found that when $\frac{1}{4}$–$\frac{1}{5}$ of the pancreas was left, the dogs could eat 500–1000 g. bread or 100–200 g. cane-sugar without glycosuria. With smaller remnants of pancreas, there was alimentary glycosuria. On the contrary, while recognizing the accuracy of Minkowski's findings, I have proved that removal of $\frac{3}{4}$–$\frac{4}{5}$ of the pancreas is always associated with an easily demonstrable lowering of the sugar tolerance. [The statement of Pflüger (13), that removal of $\frac{3}{4}$ of the pancreas without tying the

duct led to no diminution of tolerance, is incorrect, and due to faulty tests of the tolerance.] Allard (2) found that completely depancreatized dogs when injected with dextrose excrete a surplus beyond the dose injected, but incompletely depancreatized dogs do not excrete the entire quantity. On the contrary, my incompletely depancreatized dogs have excreted a surplus in excess of the dose injected.

An explanation of these results is evidently needed. In previous chapters, the effects of nervous and circulatory conditions, and the influence of other organs, have been ruled out. In the preceding chapter, the different behavior of the islands of Langerhans, according as the duct was ligated or left free, has been noted. The difference between diabetes and absence of diabetes does in fact depend upon the patency of the duct. The earliest investigators, beginning with v. Mering and Minkowski, were interested in proving that diabetes is not due to absence of pancreatic juice from the intestine; hence in their partial extirpations they ligated the ducts. Later workers, without this reason, imitated the original procedure, and thus failed to obtain a typical diabetes. Bearing in mind the results found in Chapter X, viz., that removal of $\frac{7}{8}$—$\frac{9}{10}$ of the pancreas regularly gives rise to diabetes when the ducts are left patent, the following experiments will throw light on this point.

Dog 24; female, mongrel; age 2 years; weight 6 kilos.

December 27, removal of pancreatic tissue weighing 10.2 g. Remnant about lesser duct estimated at 1 g. Remnant separated from all communication with ducts.

Poor digestion. No glycosuria at any time. Meat diet.

On January 24, 5 g. dextrose by mouth caused no glycosuria. On January 25, 10 g. dextrose by mouth caused a glycosuria of 1.65 per cent in a specimen of 136 cc. urine. On the following days up to February 1, 25 g. dextrose was fed once daily; it caused heavy glycosuria for a few hours, but never for 24 hours, and on stopping dextrose feeding the glycosuria stopped. Death occurred February 23 from inanition. The dog might have lived much longer, except for the very poor utilization of food without pancreas, and the obstinate aversion to pancreas or anything containing it. Autopsy showed only a tiny nodule of atrophic pancreas; but microscopically, well-preserved islets were found in it.

Dog 32; female, Boston terrier mongrel; age 2 years; weight 6425 g.

February 14, removal of pancreatic tissue weighing 12.4 g. Remnant about lesser duct estimated at 1.8 g. ($\frac{1}{8}$). Remnant cut off from duct communications.

Post-operative glycosuria of 0.9 per cent in 225 cc. urine. Rather poor digestion, not much loss of weight; no further glycosuria, even on bread diet.

March 4, subcutaneous injection of 10 g. dextrose; no glycosuria.

March 6–14, diet of sweetened cakes, with very slight glycosuria, ceasing promptly.

April 7, weight 6 kilos. Subcutaneous injection of 12 g. dextrose (2 g. per kilo). Glycosuria of 0.1 per cent in 150 cc. urine.

April 10, fed 6 g. dextrose per kilo on empty stomach at 9 a.m.

1 p.m., urine 50 cc., sugar 3.7 per cent.

5 p.m., urine 90 cc., sugar 0.21 per cent.

An anti-diuretic effect of dextrose was shown here.

On the following days, subcutaneous tests reported in Chapter VI further proved dextrose an anti-diuretic. The dog all this time was on diet of bread-and-meat mixture.

April 24 to May 2, similar diet, and 50 g. glucose daily by stomach-tube. Glycosuria never above 2.1 per cent; after April 29 it disappeared entirely.

May 15, dog in good condition, killed in an experiment. Autopsy showed only a few tiny atrophic nodules of pancreas, but these contained well-preserved islands of Langerhans.

If the duct had been left patent, there would have been no atrophy, and diabetes levis would have been present.

Dog 111; male, mongrel; age 3 years; weight 7050 g.

October 13, removal of pancreatic tissue weighing 16.7 g. Remnant about lesser duct estimated at 1.8 g. (less than $\frac{1}{10}$). Duct was accidentally obliterated.

Dog ate bread, also milk, without glycosuria. Mixing considerable quantities of glucose with the bread or milk caused only very slight glycosuria, ceasing promptly, and without diuresis.

October 21, dog found dead; nothing in clinical history nor in autopsy to explain reason. Pancreas-remnant weighed 2 g. No microscopic examination.

Dog 172; male, fox terrier mongrel; weight 6600 g.

December 20, removal of pancreatic tissue weighing 14.4 g. Remnant about main duct estimated at 1.3 g. ($\frac{1}{12}$). Duct cut between ligatures.

December 25, chloroformed because showing distemper. No glycosuria at any time. Pancreas remnant, completely shut off from bowel, weighed 2.6 g.

Dog 173 (see protocol); male; age 3 years; weight 10,500 g.

December 20, removal of pancreatic tissue weighing 18.9 g. Remnant about main duct estimated at 1.8 g. ($\frac{1}{11}-\frac{1}{12}$). Duct cut between ligatures and remnant separated completely from duodenum. There was a slight tendency to glycosuria at first; in particular, diet of bread-and-meat mixture caused heavy glycosuria. Other feeding experiments will require mention later.

On January 10, half of the existing pancreatic remnant was removed. There was post-operative glycosuria, which cleared up within a day. Thereafter, the dog was able to eat even bread and meat mixture without glycosuria. More than a month after the original operation, he was killed for the sake of the autopsy and to make room for other animals. The islands of Langerhans were perfectly preserved.

This record is worthy of particular notice, because the conditions of the original operation (remnant = $\frac{1}{11}-\frac{1}{12}$ of pancreas) were such as regularly cause diabetes gravis when the duct is patent. With the duct ligated, not only was diabetes absent, but it also remained absent when a second operation removed half of the existing remnant. The effect of duct-ligation is thus very striking.

Dog 171; female; age 1 year; weight 8 kilos.

December 20, removal of pancreatic tissue weighing 18.6 g. Remnant about main duct estimated at 2.5 g. ($\frac{1}{8}-\frac{1}{9}$). Duct cut between ligatures, and remnant separated from duodenum. Glycosuria was absent on diet of bread-and-meat mixture. (It is regularly present under these conditions when the duct is patent.) On January 9, most of the pancreas-remnant was removed, the remaining nodule representing only about $\frac{1}{26}$ of the original pancreas. There was post-operative glycosuria, then 2 days without glycosuria, then diabetes gravis which continued till death on

February 17. Islands of Langerhans were found absent at autopsy.

The cause of the apparently complete disappearance of the islets is open to inquiry. There may also be a question whether the disappearance was complete, since the entire remnant was not examined in serial sections. It is conceivable that the extreme over-function required of the islets in the attempt to maintain the supply of amboceptor resulted in their anatomical as well as functional break-down. The concrete lesson of this experiment, however, is that there is a minimum limit which must not be passed, even if the duct is ligated. The same lesson is taught by the following experiment.

Dog 127; male, Boston terrier; age 1 year; weight 6860 g.

October 28, removal of pancreatic tissue weighing 21 g. Remnant about lesser duct estimated at 0.6 g. (about $\frac{1}{35}$). The small duct was cut between ligatures, and the remnant dissected entirely free from the duodenum and left hanging from the vessels. Meat diet after November 2; ate nothing after November 4. Urine-record:

Date.	Quantity, cubic centimeters	Sugar, per cent.
Oct. 30	125	7.3
Oct. 31	70	12.1
Nov. 1	175	14.6
Nov. 2	575	8.1
Nov. 3	1015	4.1
Nov. 4	500	1.1
Nov. 5	250	3.
Nov. 6	200	0.1
Nov. 7	150	0
Nov. 8	200	0

Found dead, from distemper which began November 4. Pancreas remnant weighed 0.7 g.

Dog 161.

The details concerning the operations have been mentioned in Chapters XVII and XXI.

In Chapter XVII it was noted that when the pancreas is extirpated except a remnant secreting into the bowel and a subcutaneous graft, and the graft extirpated some time later, diabetes

may remain absent, even though the duodenal remnant is smaller than would suffice to prevent diabetes if the operation were performed at one session. The reason was found in the fact that in the interval between the primary operation and the removal of the subcutaneous graft, the duodenal remnant has time to hypertrophy in size and presumably also in function. A similar procedure was therefore tried with the duct ligated.

In this dog, the primary operation on November 29 left a duodenal remnant amounting to less than $\frac{1}{21}$ of the pancreas. This was presumably too small to prevent diabetes alone, but it was reënforced by a larger subcutaneous graft. On December 23 a portion of the graft was removed. On January 4 the duct of the duodenal remnant was ligated. On January 17 the last of the subcutaneous graft was removed. Glycosuria did not begin till January 22 on meat diet. It continued steadily; and on the belief that the condition was permanent diabetes gravis, the dog was sent to another department for observation. There the diet was dog-bread; yet it was reported that the glycosuria soon ceased, and was absent until, a few days before the animal's return, it reappeared in small quantity. During the first few days after her return, glycosuria was absent on meat diet; but a test made on April 4 revealed heavy glycosuria. From that time on, there was the ordinary downward course of Sandmeyer diabetes.

Transient diabetes gravis is possible when the duct is not ligated. But the disappearance of glycosuria on carbohydrate diet, with a remnant of only $\frac{1}{21}$ of the pancreas, is unheard of with a patent duct.

It is established that the blocking of the external secretion may prevent diabetes under conditions which otherwise regularly give rise to diabetes. The important question now arises whether blocking the external secretion will cause cessation of a diabetes already begun. The following experiments were performed in this connection.

Dog 176 (see protocol).

The original operation on December 28 left a remnant of $\frac{1}{8}$–$\frac{1}{9}$ of the pancreas. Diabetes levis resulted. On January 11, an additional 0.56 g. of pancreas tissue was removed; there was merely a post-operative glycosuria or very transitory diabetes gravis. On January 17, an additional 0.6 g. pancreatic tissue was

removed; the remnant now was less than $\frac{1}{13}$ of the total pancreas, and after the usual interval (with the usual absence of post-operative glycosuria), unmistakable diabetes gravis came on in full intensity.

On January 22, the duct was cut between ligatures, but nothing interposed between. The dog was starved for several days after operation, then feeding was begun cautiously, and the urine remained entirely sugar-free. Among the other animals are found a sufficient number of controls, showing that starvation of itself does not cure diabetes gravis.

Glycosuria remained absent till February 23, *i.e.*, one month after the operation of ligating the duct. The dog was very lively and gaining weight meanwhile. Then suddenly, all other conditions remaining the same, appeared heavy glycosuria, polyuria, and an abrupt change in the character of the feces. Food was withdrawn, and the glycosuria diminished. A restoration of the external secretion was considered probable, and operation on February 25 revealed a fistulous communication at the site of the main duct. It was effectively occluded, and omentum interposed. The dog once more remained sugar-free and gained weight steadily. But on March 14 a slight glycosuria appeared; without alteration in the feces. It gradually increased, and the history thenceforth was the usual downward course of Sandmeyer diabetes, till the animal was killed on May 1. Autopsy showed that the pancreas remnant had atrophied very rapidly. The sections showed no sign of any islands of Langerhans.

Dog 177 (see protocol).

The remnant was less than $\frac{1}{11}$ of the pancreas. The usual diabetes gravis ensued. Nine days after the first operation, the pancreatic duct was ligated. Glycosuria promptly diminished and disappeared, and the dog seemed as strong and lively as a normal animal. But a striking loss of weight and strength was soon evident. There was no appearance of sickness; the appetite was retained; diarrhea was absent; the feces were apparently as well digested as those of other dogs after this operation, and pancreas was fed liberally in the attempt to assist digestion and absorption. Yet even the feeding of 350 g. beef and 350 g. pancreas on January 11 did not prevent loss of weight; there was slight diarrhea after this heavy feeding, but the feces appeared not excessively bulky, mostly pasty, and reasonably well digested.

A levulose injection on January 13 was apparently well assimilated, but it did not check the advancing weakness. Death occurred as if from starvation, but starvation could never have caused death so quickly. It seems obvious that the ligation of the pancreatic duct transformed diabetes into cachexia, of pancreatic origin and unusually rapid course. The stained sections showed numerous degenerative changes in both islets and acini [see preceding chapter].

Dog 178 (see protocol).

The remnant was one-eleventh of the pancreas. The usual diabetes gravis resulted. Ten days after operation, the pancreatic duct was divided. The first urine after operation contained sugar; then for two days (January 11 and 12) it was sugar-free; than diabetes reappeared. In my opinion, feeding was begun too early in this case. It is known that the pancreas responds to the stimulation of food for several days after the duct is ligated. If this stimulation had been avoided for a longer period, till the tendency to secretion diminished and the gland had adjusted itself to the changed conditions, it seems possible that a prolonged freedom from glycosuria might have been obtained, as in the case of Dog 176. The fact that glycosuria was absent for two days seems to indicate a tendency in this direction. Investigators will probably find a higher proportion of favorable results if they allow the animals to fast for several days after ligation of the duct.

The subsequent record shows that the diabetes was permanent. On February 4, starvation was begun, in the attempt to starve the animal sugar-free, on the chance that glycosuria once absent might remain absent. Since in other animals [see below] such attempts had already ended in failure, a variation was here introduced by using phloridzin. Later I learned that Reach has employed phloridzin under somewhat similar conditions.

Reach (4) based his experiments upon the finding, by Minkowski and Hedon, that phloridzin diminishes the blood-sugar in diabetic dogs; also the fact that the carbohydrate tolerance of diabetic patients can be raised by measures that diminish the blood-sugar. He also referred to Fichera, who found that phloridzin causes glycogen formation, and to Lazarus, who claimed that it causes hypertrophy of the islands of Langerhans. Reach therefore treated a partially depancreatized diabetic dog with phloridzin, and found a reduction of the blood-sugar (originally 0.2 per cent or above 0.3 per cent) down to normal limits. But

there was no improvement in the animal's condition and no increase of sugar-tolerance.

My experiment was on a different basis from that of Reach. Most partially depancreatized diabetic animals can be starved sugar-free. Phloridzin was here used merely in the attempt to diminish the store of glycogen and glycogen-forming materials as rapidly as possible, and thus obtain freedom from glycosuria as early as possible. If freedom from glycosuria could thus be obtained, and the dog then allowed to fast for a further period, it was hoped that the pancreas might thus obtain a period of rest, which would perhaps strengthen its function so that glycosuria would remain absent on meat diet. Accordingly, this dog received phloridzin, while fasting, on February 11, 12, 17 and 18; but there was no cessation of glycosuria, and on February 22 feeding became necessary in order to save life. In the early stages of diabetes gravis with a remnant of this size and with the duct patent, it is always possible to starve an animal sugar-free. Therefore in this instance the ligation of the duct resulted in an actual aggravation of the diabetes.

Dog 184 (see protocol).

The remnant was $\frac{1}{8}$–$\frac{1}{9}$ of the pancreas. Severe diabetes ensued, the specific asthenia being perceptible as early as January 15. On that date (1 week after primary operation) the duct was ligated. The dog had received a large feeding (600 g. meat) on the preceding day, and had evidently left much of it till during the night; for at operation in the forenoon, the duodenum was found full of food and the pancreas-remnant turgid with blood. The operation was very short and easy, but there was no cessation of glycosuria. The result may be interpreted as due to the severe type of the diabetes in this case, or to the fact that the ligation of the duct was performed at the height of digestion. The latter may well have been a factor.

On February 1, starvation was begun, in the hope of obtaining sugar-freedom. On February 18, the dog seemed unable to live through the night, and yet the glycosuria was 14.6 per cent. In the hope of giving strength and perhaps a trifle of pancreatic amboceptor, the dog received a maximum transfusion from a much larger animal. She was very weak following operation, but decidedly improved the next day; but there was no cessation of glycosuria. On February 20 it was necessary to begin feeding.

Notwithstanding the initial severity of this case, experience with other dogs indicates that at this early stage they can always be starved sugar-free when the duct is patent. It therefore seems evident that the ligation of the duct was injurious in this instance. It is also worth noting once more, that the high sugar-percentages and the impossibility of starving sugar-free indicate probably a maximum diabetes, from the carbohydrate standpoint. Yet these animals recovered easily from their operations, and their wounds healed rapidly and without infection. It is therefore evident, as has been repeatedly pointed out, that the pancreas-remnant is still performing some of its functions; the absence of wound-healing and the fatal cachexia of totally depancreatized dogs are not due to the hyperglycemia nor to the loss of the carbohydrate function, but to the loss of some other pancreatic function which is preserved in the present type of diabetes, irrespective whether the duct is patent or occluded.

Dog 154 (see protocol).

This dog had been subjected to partial pancreatectomy, breaking of pancreatic nerves, and Bernard puncture; but he was not diabetic till made so by removal of additional pancreatic tissue on December 22.

One week after the operation which caused diabetes gravis, the duct was doubly ligated but not cut. The appearance of the feces indicated complete absence of pancreatic juice, but the glycosuria was not checked. Failure to check glycosuria may possibly be attributed to the preceding nerve-lesions, or to the fact that the operation was performed during digestion.

How long the duct remained closed is not known; evidently till January 7 at any rate. Autopsy later showed it to be completely restored. Starvation was begun on January 9, and was ended on January 20 when the dog seemed at the point of death; the intense glycosuria at this time is striking. It would seem that in this case the aggravation of the diabetes (so that it was impossible to starve sugar-free) resulted from the ligation of the duct, even though the duct was later restored. The case is not clear, because of preceding nerve-injuries, and doubt as to when the duct recovered patency. The point is perhaps worth investigating, and may indicate that under some conditions the simple damming up of secretion during a digesting period may result in injury to the gland, even though the obstruction is temporary. The fact

might then be brought into relation with the etiology of certain human cases of diabetes, *e.g.*, with stones or inflammation of the duct.

In this animal and with several others under similar conditions, it was observed that the urine was a normal amber when fresh, but turned black on standing. Swan has noticed a similar phenomenon with certain post-anæsthetic glycosurias. Tests for homogentisic acid with ferric chloride or Millon's reagent have given me negative results.

At autopsy, the islands of Langerhans in this dog showed the typical diabetic degeneration.

Dog 89.

The operative details concerning this animal were mentioned in Chapters XVII and XXI.

Diabetes gravis resulted from an operation on October 30. On November 22, the duct was ligated, and glycosuria continued unchecked. At autopsy, islets were found almost or entirely absent.

The following three experiments were performed to test the effects of the presence of an untied ligature.

Dog 84: male, mongrel pug; weight 7 kilos.

September 5, removal of pancreatic tissue weighing 13.3 g. Remnant about main duct estimated at 1.3 g. ($\frac{1}{11}$). Duct encircled loosely with a loop of wire, not constricting it. Urine-record, without food.

Date.	Quantity, cubic centimeters.	Sugar, per cent.
Sept. 6	125	0
Sept. 7	65	7.3
Sept. 8	475	4.1
Sept. 9	225	Heavy
Sept. 10	310	6.1
Sept. 11	235 (with vomitus)	3.6

Found dying. Abdomen found full of blood, due to erosion of a vessel by the wire. No infection. Pancreas remnant in excellent condition.

Dog 175: male, mongrel; age 3 years; weight 12,800 g.

December 27, removal of pancreatic tissue weighing 16.4 g. Remnant about main duct estimated at 1.8 g. ($\frac{1}{10}$). A ligature of heavy silk was passed about the duct without tying, and the ends left protruding outside the abdomen. Urine-record, without food.

Date.	Quantity, cubic centimeters.	Sugar, per cent.
Dec. 28	No urination	
Dec. 29	300	0
Dec. 30	480	1.6
Dec. 31	1750	1.3
	Dog pulled out ligature	
Jan. 1	1325	2.6
Jan. 2	1200	1.6
Jan. 3	550	3.1
Jan. 4	Autopsy, large quantity	3.6

Death was found due to a large abscess, resulting from the tearing in two of the pancreatic duct when the dog pulled out the ligature. Pancreas remnant well preserved; weight 2.6 g.

Dog 180: female, mongrel; age 3 years; weight 5 kilos.

December 30, removal of pancreatic tissue weighing 12 g. Remnant about main duct estimated at 1.2 g. ($\frac{1}{11}$). An untied ligature of Pegenstecher was passed about the duct, with ends protruding outside the abdomen. Record:

Date.	Quantity, cubic centimeters.	Sugar, per cent.	Diet.
Dec. 31	No urination		0
Jan. 1	70	0	250 cc. milk
Jan. 2	200	3.	90 g. meat
Jan. 3	115	10.	0
Jan. 4	340	1.9	0

Death. Autopsy shows peritonitis.
Pancreas remnant healthy; weight 1.5 g.

It is therefore evident that the simple presence of a ligature about the pancreatic duct does not prevent diabetes.

Remarks.

The experiments thus far indicate that conditions which regularly produce diabetes gravis when the duct is patent, regularly fail to do so when the duct is ligated at the primary operation. Also, under favorable conditions (Dog 176), secondary ligation of the duct appears to check a glycosuria already begun. It is desirable to learn the reasons for these facts.

It is conceivable that the ligature itself, by its irritation, might act somehow upon the pancreas remnant or its nerves, as Pflüger supposed ligatures might do. The above experiments with Dogs 84, 175 and 180 probably rule out this possibility as far as it can be ruled out by an untied ligature. Also, it might be imagined that the pancreas, weakened by removal of most of its tissue, becomes subject to infection through its duct, and therefore diabetes occurs when the duct is patent and not when it is ligated. It is true that infection has been thought of in the etiology of human diabetes; Senator (1) discusses it seriously; Lepine [(1), pp. 402–3] mentions the opinion of Teissier and Charrin that diabetes may be due to an infection through the duct of Wirsung; similar ideas will be found in the paper of Gelle; Hirschfeld (2) has lately emphasized the rôle of infection, as evidenced by swelling of the liver; and though the above views are not general, it is commonly accepted that in case of stone, infection through the ducts may play a part in producing diabetes. Nevertheless, the microscopic examination of the pancreas remnant in the animals I have studied does not give the impression of duct-infection as the cause of their diabetes, and the possibility of this as the determining factor may with fair probability be ruled out.

The effects due to duct-ligation must have origin in one of two places, either (*a*) in the intestine, or (*b*) in the pancreas. It is desirable to reflect upon all the possibilities, however remote, whereby the stopping of the external secretion of the pancreas could either influence intestinal processes, or alter the pancreas itself, in such manner as to produce this striking effect upon the glycosuria.

(*a*) At least three possible influences proceeding from the intestine may be thought of as follows: (1) an effect upon digestion; (2) a specific intestinal secretion; (3) a specific substance or substances contained in the pancreatic juice.

(1) Minkowski [(1), p. 97], in discussing the pancreatic cachexia, which Hedon called "diabetes without glycosuria," suggested that it might be due to altered digestion. De Domenicis has contended from first to last that diabetes is connected with the absence of pancreatic juice from the intestine. Arany and others have published theoretical suggestions that diabetes is due to disturbance of intestinal conditions. Funck in particular holds the opinion that diabetes is due to absorption of intestinal toxins; others [see Forcheimer, p. 159] have expressed similar views. Treatment of diabetes by means of yeast preparations [see Chapter XVIII] and by various measures directed to the intestine, has been attempted. The idea in most of these cases has been that intestinal conditions cause diabetes; but our search just at present is for the opposite thing, viz., for intestinal conditions which may prevent diabetes. Two such conditions may possibly be imagined. First, it may be supposed that glycosuria ceases merely from malnutrition, due to impaired digestion and absorption following exclusion of pancreatic juice. This supposition is absolutely excluded by the fact that Dog 32 lived in excellent condition for a long period, and that Dog 161 gained weight while sugar-free; also that diabetic dogs under similar conditions (Dog 178, Dog 184) were starved to the verge of death without cessation of glycosuria. Second, it may be supposed that digestion is qualitatively altered by absence of pancreatic juice. For example, it is known that digestion is carried farther in the intestine than in the stomach; amino-acids are found in the intestine, not in the stomach [see Abderhalden, Klingelmann and Pappenheim]. Text-books admit that protein may to some extent be absorbed in the form of albumoses and peptones. Nolf (1) has even asserted the belief that only polypeptids, peptones and albumoses are synthesized into albumin in the body, and that the amino-acids are entirely burned. At any rate, it might be imagined that in the absence of pancreatic juice, the splitting of protein (by pepsin plus intestinal juice) is either qualitatively different or quantitatively less complete than when pancreatic juice is present. It might thus arise that a larger proportion of protein is absorbed in the form of albumoses, peptones, polypeptids, or in some other form different from that when pancreatic juice is present. Amino-acids are known to be convertible into sugar; it may be that the tendency to such conversion is less when nitrogen is absorbed in higher compounds; and it may be that the diabetic organism can supply its

needs from these higher nitrogen compounds without glycosuria, when the same amount of nitrogen in the form chiefly of amino-acids would give rise to glycosuria. All that can be said concerning such speculation is that it is improbable. Tests based upon chemical differences in the fecal nitrogen, as a method for diagnosing absence of pancreatic juice from the intestine, have not proved successful. But we are perhaps not able to exclude entirely the possibility that prevention of glycosuria by ligation of the pancreatic duct may be due to some modification of the processes of digestion.

(2) It is also possible to imagine that some specific function of the intestine (especially the duodenum), in the form of either an external or an internal secretion, may be concerned in this matter. Roger and Garnier have called attention to a special toxicity of the duodenal contents. On the other hand, there are scattered suggestions classifying the duodenum as an organ of internal secretion. Maury advanced the possibility that it secretes something essential to life. S. A. Matthews found that closure of the pylorus with a short-loop gastro-enterostomy is harmless for dogs, but with a long loop (opening 35–40 cm. from pylorus), though they recover from the immediate operation, there is rapid loss of weight, great appetite and thirst, very poor digestion, and death from cachexia, the duration of life being only about a week longer than after pancreatectomy. He found total extirpation of the duodenum to be incompatible with life, and explained the results of Minkowski (7) and others as due to failure to remove the entire duodenum. On this basis he suggested the existence of an internal duodenal secretion, perhaps furnished by Brunner's glands. At any rate, the cause of the conditions described by Matthews is unknown. They resemble pancreatic cachexia. It is conceivable that the duodenum possesses unknown functions, and that these modify and are modified by the pancreatic function. Further evidence on the subject is lacking.

(3) The pancreatic juice itself may contain some substance tending to produce glycosuria. The glycosuria produced by Pariset and others by intravenous injection of pancreatic juice is presumably non-specific. Loeper and Esmonet found that absorption of pepsin and pancreatic ferments — especially when the intestinal mucosa is inflamed — and still more the injection of these ferments into a mesenteric vein, produces irritation of the liver, diminution of glycogen, and increased secretion of bile.

But the most direct evidence was furnished by Sandmeyer. He found not only that pancreas-feeding increases glycosuria, or produces it in dogs not otherwise glycosuric, but also [(2), p. 40] diacetic acid appeared in the urine only when pancreas was fed. Leschke (1) reviewed the literature showing that increase of glycosuria is the rule from feeding of pancreas to diabetic patients or animals. Reach has verified this phenomenon, but has detracted from its apparent specificity, by showing that any kind of raw meat has the same glycosuric effect as raw pancreas. Chapter IX was devoted entirely to this subject, and there it was shown that food plays an important part in the production of various forms of glycosuria; that diabetic patients may be affected very differently not only by different forms of carbohydrate but also by different forms of protein; and on the contrary certain foods, notably oats, may frequently be assimilated with surprisingly little glycosuria. That chapter was written chiefly because the relations between the internal and external pancreatic secretion seem to afford a rational explanation of the behavior of oats and other foods.

(*b*) Influences proceeding from the pancreas itself are intrinsically more probable than influences proceeding solely from the intestine. Such influences resulting from ligation of the ducts may be thought of as follows: (1) Absorption of external secretion; (2) Circulatory, nervous, and humoral changes; (3) Participation of acini in internal secretion; (4) unknown influences.

(1) In case of stasis of the external secretion, this secretion is absorbed. In Chapter II were mentioned the researches showing that the blood-diastase is increased by ligation of the pancreatic ducts [Wohlgemuth, Otten and Galloway, Gould and Carlson, Clerc and Loeper, and others]. Lepine [(1), pp. 175–76] has found the glycolytic power of the blood increased either by ligation of the pancreatic duct or by stimulation of the pancreatic nerves. Absorbed substances, especially trypsin and steapsin, are held responsible for the toxic symptoms and fat-necrosis which follow various pancreatic lesions. [See von Bergmann, Fischler, Rudolph, Polya, and Rosenheim and Shaw-Mackenzie.] We are ignorant of the effects of these substances when absorbed in smaller quantities. Bamberg supposes absorbed trypsin to be neutralized by the anti-tryptic power of the blood; this power is increased by injections or by intra-peritoneal autolysis. Battelli

and Stern studied the effects of trypsin upon oxidations in animal tissues, and found that it diminishes tissue respiration. The anti-tryptic power of the blood, and particularly of diabetic blood, has been the object of considerable investigation [see Neisser, Neisser and Koenigsfeld, etc.]. Marcus has claimed in a number of human cases an inverse relation between sugar and anti-tryptic power; when sugar is high, anti-tryptic power is low; and vice versa. Other unknown constituents of the pancreatic juice might be thought of. Wohlgemuth (1 and 2) has found in it a hemolysin of the nature of a pro-lecithid; and it will probably be admitted that the pancreatic juice is something which we still understand very poorly. But, in general, these considerations are purely speculative. The diastase and glycolytic ferment of the blood stand in no relation with diabetes, and there is at least no evidence that absorption of the ferments of the external secretion has any effect in preventing diabetes.

(2) Circulatory, nervous and humoral influences are possibly important. The circulation is changed after duct-ligation; the vessels become narrowed and tortuous, and the circulatory alterations due to digestion are probably much diminished. It is possible that these circulatory conditions favor the function of the islets, and that thus a better supply of internal secretion is maintained. Also, Pflüger considered that embryology indicates an important rôle of the duodenal nerve-plexus in regulating and coördinating the work of the pancreas and related organs. Natus saw degeneration of the pancreatic nerves after ligation of the duct. But it is especially in regard to digestion that all factors, circulatory, nervous and humoral, come into play. They are known to influence the external function very powerfully, and an effect upon the internal function is possible. It is conceivable that there is some sort of alternation between the internal and external secretion; relief from the duty of external secretion will then permit a more continuous production of internal secretion. Moreover, the external function of the pancreas adapts itself to some extent to the kind of food, and there is the possibility of some kindred regulation of the internal secretion. The humoral regulation by means of secretin, discovered by Bayliss and Starling, has been attacked by Popielski (1) and Lombroso (12), but is defended by Gley, Zunz (2) and others, and is generally accepted. The nervous regulation has been emphasized especially by the Pawlow school. Lombroso (15) investigated the secretory conditions in pancreatic

grafts after cutting the pedicle. Bickel has reviewed the various agencies influencing pancreatic secretion, including the effects of drugs; and Frouin (1) has studied the effects of sugars as well as nitrogenous substances in modifying the secretion produced by HCl. Ssawitsch, and Babkin and Ssawitsch, have described two kinds of pancreatic juice, in relation to the two governing mechanisms, one through nerves, the other through the blood. Especially interesting are the specific effects produced by various foods. According to Wohlgemuth, the flow from a pancreatic fistula is markedly increased by carbohydrate food, slightly increased by protein, and not much affected by milk or fat. Glaessner and Popper opposed Wohlgemuth's findings; Kempf's results were also different. London and Lukin found that fat-feeding produces the largest quantity of both bile and pancreatic juice, albumin considerably less, while carbohydrate produces by far the smallest bile-flow and a pancreatic flow not much different from albumin. Smirnow has found the pancreatic secretion stimulated by fat. The work of Cohnheim and Klee is of preëminent importance in the present connection. They worked with dogs provided with fistulæ in such manner that substances (frequently after gastric digestion in another dog) could be introduced directly into the duodenum, and the bile and pancreatic juice obtained separately. Witte peptone and pure oil both had no more effect than water in stimulating pancreatic secretion. But soap, which arises from the fat, is a powerful stimulant of pancreatic secretion. Meat-extract had no more stimulating action than water; meat therefore increases pancreatic secretion only indirectly, by stimulating gastric secretion. They confirmed on a more accurate basis the observation of Best, that flour, or dough ready for baking, produces a far smaller flow of pancreatic juice than the bread baked from it. Bread was the most powerful pancreatic stimulant in a series of carbohydrate foods; potatoes came next; wheat flour was much less, and finally oat-meal was by far the least active stimulant of all. The authors rightly apply their discovery to the problem of the oat-cure in diabetes; it corresponds perfectly to the fact that oat-meal generally produces a minimum of glycosuria; that bread may produce intense glycosuria though gruel made from the same flour may be perfectly assimilated; that addition of other foods, especially meat, spoils the benefits of the oat-cure, etc. They also justly view their experiments as indicating some sort of opposition or balance between the internal and external

pancreatic functions. It is true that the relations found are not absolute; for example, fats (through soaps) stimulate the external pancreatic secretion, but do not increase glycosuria in diabetes. Qualitative differences may perhaps be indicated. But the net result of all such studies is to show the complex control under which the external pancreatic function stands, and some sort of regulation of the internal function is not improbable. The relations between the internal and external pancreatic secretion, and the important regulation of the pancreas by food and by influences from the duodenal mucosa, furnish a better explanation of the oat and other cereal "cures" than any of the older hypotheses discussed in Chapter IX. The effects of duct-ligation may be looked upon as somewhat analogous but more powerful.

(3) Participation of acini in internal secretion. First, it is conceivable that the prozymogen substance, if not formed into ferment and discharged externally, may be absorbed into the blood and play a part in the internal function of the gland. Prozymogen granules are often visible months after ligation of the ducts, and some have supposed that they must be of some use or they would disappear. Second, it is known that duct-ligation leads to a slow atrophy of the pancreas. In this process, cells are constantly being destroyed and their substance absorbed, and it is possible that the substance of these cell-bodies furnishes a supply of internal secretion, until finally the cells are nearly all destroyed and diabetes of the Sandmeyer type ensues. This supposition is not very probable; for of two dogs with pancreas-remnants of equal size, the one with the higher sugar-tolerance is not the one whose pancreas is undergoing more rapid atrophy, but rather the one whose remnant remains better preserved. Third, it is an attractive supposition that the cells which ordinarily produce the external secretion are able, when the external function is abolished, to direct their energies to the production of internal secretion. Though the islets are presumably specialized for the internal function, yet the conception of them as an independent organ or tissue has been shattered. They may at any time be produced from the same ducts that give rise to acini; apparently the conditions of the moment decide whether a given duct-cell shall become an islet cell or an acinar cell. Though the energy of the acinar cells under normal conditions is presumably devoted chiefly or entirely to the external secretion, it is possible that this activity varies. Excessive activity of the external function, marked in

diabetic dogs by hypertrophy of the acinar tissue, may be attended by abolition of whatever small part they may contribute to the carbohydrate economy. A resting condition of the acinar cells, or especially the abolition of their external function by duct-ligation, may cause them to assume more or less of an internal function. On this basis such results as reported by Pratt, and by Milne and Peters, receive explanation; the cells that persist may be acinar cells, but they are under abnormal conditions. Diabetes is at present divided into hostile camps, each supporting its own facts and denying the facts of opponents. In this and all other phases of the subject, it is probable that the true and ultimate understanding of the matter will find a place for all the facts and will harmonize their apparent discord. Though the insular hypothesis is essentially correct in regarding the islets as the specialized tissue preëminently subserving the internal carbohydrate function of the pancreas, it still remains possible that the acinar cells have at least a latent power of this sort, and that it may be possible to take advantage of this power through duct-ligation. The importance of nervous or other controlling forces must also be recognized, as indicated by the failure of duct-ligation to check diabetes in dogs when the condition has been allowed to persist too long, even though a considerable mass of acinar tissue and some apparently well-preserved islets still remain.

(4) Other possible influences must be classified as simply unknown. Bruckner and Jianu, also Glaessner and Pick, found adrenal changes after pancreatic fistulæ; Minami has found them in a few cases. We do not know the reason for this occasional result. Again, there is the remarkable fact that, though a carefully ligated and resected pancreatic duct may restore itself, yet if the duct is cut across and left free in the peritoneum, the result is not a secretion into the peritoneum and consequent death, but a cessation of secretion as complete as if the duct were effectively ligated. This behavior is unique among the glands of the body. Lombroso (12) found that if the portion of duodenal mucosa surrounding the opening of the pancreatic duct is destroyed with the thermo-cautery, the secretion gradually diminishes and finally stops altogether, although the opening and the entire length of the duct be entirely patent. The prevention of glycosuria by ligation of the duct is therefore only one of a number of peculiarities and unknown aspects of the pancreatic function and regulation.

According to Kyrle, isolation of pancreatic tissue is a stimulus giving rise to certain regenerative processes; it may be that these are a factor in raising the sugar-tolerance.

All the above speculative possibilities and questions can be decided only by experiment. The principal question is whether the presence or absence of glycosuria is due to presence or absence of pancreatic juice in the bowel, or whether it is due to changes in the pancreas itself. The first experiments are concerned with pancreas-feeding. Fresh beef pancreas was used in all cases. Notice should also be taken of the fact that in the records already presented (Dogs 154, 176, 177, 178, 184) pancreas-feeding has had no *beneficial* effect other than for digestion; it has never prevented or diminished either glycosuria or cachexia.

Dog 171.

This animal has been previously mentioned in this chapter.

The remnant left by the operation of December 20 was $\frac{1}{8}$–$\frac{1}{9}$ of the pancreas, and (contrary to the rule when the duct is patent) the animal was able to eat bread-and-meat mixture without glycosuria.

On December 29, 100 g. pancreas was added to the standard diet of bread-and-meat mixture. There was no glycosuria till January 1; then it was heavy, and the next day still heavier. The delay of glycosuria is not unusual; it is a fairly common occurrence, both in human and in animal cases, that a diet which does not produce glycosuria the first day may produce it if continued for several days. The reason is presumably a gradual using-up of an existing reserve-store of pancreatic amboceptor.

On January 2, a diet of 600 g. meat caused prompt disappearance of glycosuria. It remained absent on the following days while the meat was gradually being replaced by pancreas, till on January 5, the feeding of 600 g. pancreas resulted in a glycosuria of 2.8 per cent, with marked polyuria. In other words, this dog which could eat bread-and-meat mixture without glycosuria, became markedly glycosuric when fed on pancreas. On January 6 and 7 the amount of pancreas was diminished, and the glycosuria diminished. But on January 8 the full 600 g. pancreas was fed (with 150 g. left from the day before) and the result was only a faint glycosuria. Two facts here arouse the suspicion that pancreas has not a specific effect, that it is not a true diabetogenous substance: (1) its effect is irregular, and "immunity" rather than

lowered tolerance results; (2) it causes the dog to gain instead of to lose weight.

Dog 173 (see protocol).

This dog has also been mentioned previously. On December 20, $\frac{10}{11}$ of the pancreas was removed and the duct ligated. December 25, a diet of bread-and-meat mixture was begun, and resulted in heavy glycosuria, but glycosuria quickly disappeared when the diet was changed to meat (December 27–28). On December 29–31, 100 g. of the meat was replaced by pancreas, and there was slight glycosuria, with polyuria. On January 1, the proportion of pancreas was increased by 100 g., and the glycosuria reached 1.7 per cent. But glycosuria then diminished as the pancreas was increased, and the feeding of 700 g. pancreas on January 3 resulted in no glycosuria at all. The weight was rapidly rising meanwhile, and it is possible that the disappearance of glycosuria was due to the improved general nutrition.

After the second removal of pancreatic tissue (January 10) tolerance was not diminished; on the contrary, the animal was now able to take pancreas and also bread-and-meat mixture without glycosuria. Beginning January 22, pancreas and bread-and-meat mixture were fed together, with the result that glycosuria finally appeared on January 25.

Dog 48; female, bull terrier; age 1 year; weight 9 kilos.

July 5, removal of pancreatic tissue weighing 15.2 g. Remnant communicating with main duct estimated at 4 g. No diabetes.

July 15, after continuous freedom from glycosuria on bread diet, fed 400 g. fresh beef-pancreas. No glycosuria.

July 16, given 1500 g. pancreas; part eaten voluntarily, balance fed forcibly. Part vomited. No glycosuria.

July 18, sick, with distempered nasal discharge. Autopsy showed acute pneumonia and old purulent pleurisy. Pancreas-remnant healthy; weight 7 g.

The above experiment was undertaken to test whether any quantity of pancreas feeding will cause glycosuria when the duct is patent. It is not fully conclusive because the pancreas-remnant was too large.

Dog 38.

August 2, partial pancreatectomy was performed, leaving a remnant of $\frac{1}{7}$–$\frac{1}{8}$ of the gland. Since the duct was patent, the resulting condition was diabetes levis. On August 5, the feeding of

raw veal was begun. After 400 g. on August 6, the urine of August 7 showed a high sugar-content. The same was true after the feeding of 400 g. raw beef on August 7. The glycosuria promptly disappeared on reduced diet, and did not reappear till after 250 g. raw beef on August 12; but after repetition of this same amount on August 13, the urine of August 14 was sugar-free. Thereafter, raw beef failed to produce glycosuria, even in the quantity of 500 g. on August 16. On August 17, bread-feeding resulted in prompt glycosuria, but raw beef failed to make it continue.

In all experiments except as otherwise recorded, the meat fed to all these animals was well cooked. Also, the meat contained in the bread-and-meat mixture was always cooked. The glycosuria observed from feeding raw meat in this instance might be taken to confirm Reach's statement that raw meat of any kind has the same glycosuric effect as raw pancreas; the mere improvement of digestion as the causal agent is thus ruled out. Also, it would tend to show that this glycosuric effect is obtainable when the pancreatic duct is patent. The raw veal which caused the first glycosuria had been repeatedly extracted with water (on ice), and pressed in the meat-press. Since its glycosuric effect was apparently equal to that of fresh raw beef, there is here some degree of evidence that the glycosuria is not due to the extractive substances of the meat.

I prefer, however, to draw no conclusions. This animal's record might be satisfactorily explained as a simple case of transient diabetes gravis. As is well known in human diabetes, there may be a limit of assimilation for protein as well as for carbohydrate, and such was possibly the case in this animal.

It may be noted that a somewhat similar condition was observed in Dog 154, viz., absence of glycosuria from 200, 400, 500 g. meat on November 28, 29, 30, and presence of glycosuria when the diet was 750–1400 g. meat. And here the meat was *cooked*.

Dog 80.

This was an animal with partial pancreatectomy, patent duct, and transient diabetes levis. On September 16, glycosuria on bread-and-meat diet was just on the point of disappearing. On that day, 300 g. horse-pancreas was added to the diet. Glycosuria promptly disappeared; the result was perhaps favored by the fact that with the pancreas the dog ate less bread-and-meat mixture than previously.

On the whole, I doubt if any effect from feeding pancreas or raw meat can be demonstrated when the duct is patent. Certainly, an increase of glycosuria such as observed by Sandmeyer (5 to 14 fold) will never be obtained with a patent duct. This may therefore stand as one more difference between the conditions with and without closure of the duct.

A question of considerable interest in the present connection is in regard to the condition resulting when an animal has two pancreatic remnants, one ligated, and one secreting into the bowel. Will the ligated one protect from diabetes, or will the presence of the secretion of the other remnant in the intestine suffice to cause diabetes? Or is there a relation of size between two such remnants; will diabetes be absent when the ligated remnant is much larger than the other, and present when the secreting remnant is the larger? The following experiments apply to this problem.

Dog 97; female; age 11 months; weight 12 kilos.

September 27, removal of pancreatic tissue weighing 26.9 g. Remnant estimated at 2:6 g. (less than $\frac{1}{11}$) left in connection with a small duct. This was perhaps supernumerary, not communicating with the greater part of the remnant; for at autopsy the main mass of the remnant appeared as a few extremely atrophic nodules, while the tiny fragment secreting into the bowel weighed only 0.2 g. If the remnant had communicated with the duct, diabetes gravis would have been inevitable. As it was, beginning October 2, the dog was able to eat large quantities of bread without glycosuria. Absence of glycosuria was not due to failure of digestion and absorption, for the weight increased. Addition of glucose to the diet October 5–8 caused heavy glycosuria; meat diet on October 9 caused its prompt disappearance; it reappeared when the dog was fed plain bread-and-meat mixture on October 10, then ceased on a continuance of this diet. Beginning October 15, glucose was mixed with the feed, but even so, the glycosuria was irregular (absent on October 16, 18, and 24). Weight was gained on the sugar diet, but the sugar-tolerance was perhaps damaged, for after October 24, a plain bread-and-meat diet produced glycosuria. This disappeared when the diet was changed to (cooked) meat.

On October 30, instead of 1500 g. meat, the dog was fed 750 g. meat and 750 g. raw pancreas. The result was glycosuria of

0.5 per cent. When a kilo of pancreas alone was fed on October 31, no glycosuria resulted; likewise when 1500 g. pancreas was fed on November 1. On November 2, feeding of 750 g. horsemeat and 750 g. pancreas again caused glycosuria. But on November 3, the feeding of 750 g. pancreas with 750 g. (cooked) beef caused no glycosuria. On November 5, the feeding of pancreas and horsemeat again caused glycosuria. In this experiment it is seen that horsemeat alone, or pancreas alone, or pancreas with beef, produced no glycosuria; but pancreas with horse meat regularly produced glycosuria. It would seem that the glycogen of the horsemeat was the determining factor here.

The experiment as a whole shows that if the non-secreting pancreas remnant is sufficiently large and the secreting remnant sufficiently small, the result may be the same as if the whole remnant were ligated. Digestion was not much better in this dog than in those with total ligation; diabetes was prevented; and the glycosuric tendency of pancreas-feeding was demonstrable.

Dog 143.

The operative procedures were mentioned in Chapters XVII and XXI. The case is complicated by the fact that the animal was also used for sugar-puncture, but this probably was without essential influence in this case.

The net result of the operations of November 9, November 29, and December 8 was that there were two pancreas remnants, each communicating with a duct, and the dog was not yet diabetic. On December 21, additional pancreatic tissue was removed, and the duct of the smaller remnant was ligated. The result was diabetes gravis. On December 29, the duct of the other remnant was ligated, but the diabetes was not checked. Pancreas feeding was without special influence. On January 9 starvation was begun, but glycosuria did not disappear until the dog was too weak to recover.

If both ducts instead of one had been ligated in the operation of December 21, diabetes would presumably have been prevented. With the smaller remnant ligated off, and the larger one secreting into the bowel, diabetes was not prevented.

Dog 104 (see protocol).

The operation of November 27 left two pancreas-remnants, each communicating with a duct; also shreds of appreciable size

isolated except for their vascular supply. Diabetes gravis resulted. Ligation of the duct of the principal remnant on December 8 did not stop it; but there was apparently some effect, viz., absence of glycosuria on December 10, glycosuria of only 0.7 per cent on December 11 (after 200 cc. milk the day before), and on the following days a lower sugar-percentage than before operation. The effect was transitory, for the glycosuria steadily increased. On December 21 the other pancreatic duct was ligated, with resulting death from gangrene of the duodenum.

Dog 155 (see protocol).

Although the remnant was close to $\frac{1}{6}$ of the pancreas (the estimate is probably rather high), diabetes gravis resulted. On December 5, the position of the remnant was shifted, and about a third of it was separated from the duct. There was no effect upon the glycosuria. On December 23, the pancreatic duct was divided. Death occurred from peritonitis, without cessation of glycosuria.

As previously mentioned, many operators have observed no glycosuria after supposedly total extirpation of the pancreas, and the reason has been the inadvertent leaving of very small shreds of pancreatic tissue. If such shreds are able to prevent glycosuria when all the rest of the pancreas is removed, it is of interest to know whether they can prevent glycosuria when there is a pancreatic remnant secreting into the bowel.* The following experiments pertain to this question.

Dog 96; female, Boston terrier; age 11 months; weight 8825 g.

September 26, removal of pancreatic tissue weighing 16.2 g. Remnant about lesser duct estimated at 2.2 g. ($\frac{1}{8}$–$\frac{1}{9}$). Isolated shreds of pancreatic tissue were purposely left along the pan-

* Milne and Peters (1) report that they have found diabetes absent when they removed the entire pancreas except a piece the size of a pea secreting into the bowel. This remnant showed great hypertrophy, and the islets nearly or completely disappeared. I can account for the absence of diabetes only on the supposition that other small fragments were left, isolated from the bowel. In my experience, hypertrophy of acinar tissue with deficit of islet tissue has meant that the anti-diabetic power of the tissue showing such changes is deficient or lost. There may still be some slight possibility that different operative methods, especially different nerve-injuries, may explain. The question is important to investigate, since those influences which account for the occurrence or non-occurrence of diabetes in animals may point the way to the cure or prevention of human diabetes.

creatico-duodenal vessels. Glycosuria was absent even on bread diet. The tolerance was rather low, as was proved by mixing sugar with the feed; but on October 6, a subcutaneous injection of 20 g. dextrose was perfectly assimilated (on bread diet). On the same diet, on October 7 a subcutaneous injection of 50 g. dextrose caused an excretion of 6.4 g., and the same dose on October 8 caused an excretion of 3 g. In this case the impression is given that the small scattered shreds prevented diabetes and conferred a considerable tolerance.

Dog 93; male, French bull; adult; weight 8400 g.

September 21, removal of pancreatic tissue weighing 21.2 g. The most of the remnant was a mass communicating with the lesser duct; but a number of isolated shreds were also left along the vessels. Total remnant estimated at 2.6 g. ($\frac{1}{9}$).

The size of the remnant was such as to insure diabetes levis or perhaps diabetes gravis under ordinary conditions. But this dog was able to live on bread without glycosuria. Here also the impression is given that the scattered shreds of pancreatic tissue had a well-marked effect upon the assimilative power.

Dog 88; female, Skye terrier; adult; weight 6920 g.

September 13, removal of pancreatic tissue weighing 11.9 g. Remnant about main duct estimated at 0.9 g. Also scattered shreds were left along the splenic and pancreatico-duodenal vessels; their total weight was guessed at 0.75 g.

The urine on September 14–15 was negative as usual; on September 16 began permanent diabetes gravis, of the usual severity. Here the secreting remnant was small enough to permit diabetes gravis, but the total weight of pancreatic tissue, counting the scattered fragments, was large enough to have prevented it. Diabetes gravis ensued, and it is evident that in this instance the scattered fragments were without important influence.

Dog 89.

The details have been mentioned in Chapters XVII and XXI. The operation of September 17 left a total remnant of slightly more than one-seventh of the pancreas, equally divided between a secreting duodenal fragment and a subcutaneous graft. For the most part, the animal was able to live on bread without glycosuria — something probably not possible if the entire remnant had been

in communication with the bowel. There is an impression that perhaps the isolation of part of the remnant from the bowel increased the tolerance.

Dog 161.

Details were mentioned in Chapters XVII and XXI.

In the operation of November 29, nerves were broken, but as shown in Chapter XVII, no diabetogenous effect is thus produced. The total remnant was $\frac{1}{5}$–$\frac{1}{6}$ of the pancreas, mostly in the form of a subcutaneous graft. Bread diet generally caused considerable glycosuria; the tolerance was thus lower than in Dog 89 (where the fraction of pancreas was smaller). The impression is given that the subcutaneous graft perhaps failed to contribute its full share toward keeping up the tolerance.

An experiment which would appear crucial for the question whether the effect upon glycosuria proceeds from the pancreas or from the bowel, is the establishment of a pancreatic fistula. But it is not necessarily crucial, because any sort of interference with the duct or with the natural excretory process may be followed by changes in the gland. The best method would doubtless be to remove the portion of duodenal mucosa surrounding the orifice of the duct, and bring this out to the skin. I have not used this method. My only fistula experiment was the following.

Dog 38.

Details were mentioned in Chapters X and XX. The dog had diabetes gravis dating from operation on September 14.

On October 7, the pancreas remnant was separated from the intestine and caused to secrete through a fistula. The dog lived six days thereafter. Glycosuria did not cease, except through weakness. The experiment is inconclusive, and the series could not be continued.

Summary and Discussion.

The question may be reviewed in the following divisions: (*a*) pancreas feeding experiments; (*b*) experiments with divided remnants; (*c*) fistula experiments; (*d*) experiments with duct-ligation; (*e*) application.

(*a*) *Pancreas Feeding Experiments.*

The glycosuric effect of pancreas feeding, as reported by previous authors, has been confirmed; but it has been found less marked, or perhaps altogether absent, when the pancreatic duct is patent. The reason for this difference is unknown. Human patients are known to vary in susceptibility. When the glycosuric effect is present, there are reasons for supposing that it is in one sense non-specific, in another sense specific. First, the effect is non-specific in that it is not limited to pancreas-tissue, but is produced, as Reach has shown, by any form of raw meat. The improved digestion resulting from the pancreas-enzymes may be an additional factor. Second, the effect is possibly specific in that the influence, whether from pancreas, raw meat, or any other food, is possibly exerted upon the pancreas. Opposed to this idea is the fact that the animals gain weight and in some cases develop "immunity." But the former may be explained by improved digestion; the latter may represent an efficient response of the pancreas-remnant to this stimulus. Here it may be advisable to bear in mind the claim of Pratt and Spooner, that under certain conditions (perhaps before the tolerance has dropped too low or the pancreas lost power to respond?) pancreas-feeding may raise the sugar-tolerance. In favor of the idea of a specific influence upon the pancreas is the fact that the glycosuria due to pancreas-feeding is generally accompanied by polyuria. The hypothesis is convenient as a simple, unified explanation of a series of otherwise puzzling facts, viz., the tendency of certain foods, especially certain proteins, to aggravate glycosuria, and also the remarkable power of assimilation of certain foods, notably oats, other cereals, and even pure dextrose. These facts were reviewed in Chapter IX. It is remembered that cereals lose their beneficial effects if given with even a small quantity of meat, and even oats must be given in boiled form, for if baked the virtue is lost. All these facts find a ready explanation if we assume that different foods stimulate the pancreas differently. That they stimulate the external function differently is now well established. An effect upon the internal function may be conceived as direct, viz., a specific adaptation of this function to the food; or it may be conceived as indirect, viz., as influencing the internal function through its influence upon the external function, since these two functions apparently stand in some sort of relation. On this

basis the whole matter becomes less strange, and it is possible even to understand that a boiled cereal may have a different effect than a baked cereal.

(*b*) *Experiments with Divided Remnants.*

The best form of such experiments is probably furnished by animals each having two pancreas-remnants, one surrounding each duct. Either can then be ligated as desired. I regret that distemper and other difficulties prevented a longer series on my part. The series presented, including those with subcutaneous grafts, has yielded discrepant results. This is to be expected. When the duct is left undisturbed, diabetes loses its uncertainty and its mystery; removal of a definite proportion of pancreatic tissue is followed by a definite grade of lowered sugar-tolerance or diabetes, and irregularities are, broadly speaking, eliminated. But it has long been notorious that the effects of partial pancreatectomy, with ligated ducts, are widely irregular and uncertain. Accordingly, in dealing with animals having two pancreas-remnants, one secreting into the bowel and the other not, we are dealing with two factors, one regular, the other irregular. Sometimes a ligated remnant (or subcutaneous graft) remains well preserved and keeps up a high sugar-tolerance. At other times it (or its islet-tissue) rapidly degenerates and benefits the tolerance very little. These irregularities naturally lead to irregular results in such experiments; it would be highly important if we could learn their cause. But positive results carry greatest weight for the present question; and some of these seem to indicate that diabetes may be absent with one remnant secreting and the other ligated, when it would be present if both remnants were secreting into the bowel. The question of possible relations of size between these two remnants is also important.

(*c*) *Fistula Experiments.*

These can be crucial only when positive. That is, if diabetes occurs when a pancreas-remnant is allowed to secrete, irrespective whether its secretion escapes into the intestine or through an external fistula, we then know that the diabetes is due not to the presence of pancreatic juice in the bowel, but to some effect of the secretory process in the pancreas itself. On the contrary, if diabetes is prevented, or stopped after beginning, by the establishment of a fistula, it is then uncertain whether the difference is

due to the absence of pancreatic juice from the bowel, or to alterations in the gland produced by the fistula. My attempt (Dog 38) to check diabetes by establishment of a fistula gave a negative result. The question may be considered settled by the observations of Minkowski, already described; viz., two dogs with subcutaneous grafts, one secreting freely, the other atrophic and secreting poorly; the former animal had intense diabetes; the latter was free from diabetes. In the latter animal, the internal function of the graft resembled that of a ligated fragment. In the former animal, diabetes occurred just as though the remnant were secreting into the bowel. Therefore, the cause of diabetes when the duct is patent, and of its absence when the duct is ligated, is not the presence or absence of pancreatic juice in the bowel, but is some relation between the external and internal secretion in the gland itself. The organic basis of the opposed results may be the preservation of the islands of Langerhans in one case and their destruction in the other. The nature of the influence which gives rise to this difference is still unknown.

(*d*) *Experiments with Duct-Ligation.*

A number of concordant experiments have shown that ligation of the duct regularly prevents diabetes under conditions which regularly produce diabetes when the duct is patent. Some of the confusion of the previous literature is cleared up by this discovery. The phenomenon is perhaps most striking in the case of Dog 173, in which ligation of the duct not only prevented diabetes with a size of remnant which regularly permits diabetes, but also prevented it when half of this remnant was removed. A more accurate study of the curve of dextrose tolerance in such animals is desirable. Apparently, the tolerance is low just after operation, and rises thereafter, sometimes attaining a rather high level. After a longer or shorter period, it begins to fall, and the inevitable end is the Sandmeyer type of diabetes.

There is also evidence indicating that a glycosuria already begun may under favorable conditions be checked by ligation of the duct. If conditions are not favorable, the duct-ligation apparently may aggravate the diabetes. The importance of such experiments is evident. Unfortunately, they were just under way when it became imperative to stop the research. The results obtained with Dog 176 seem, however, strong enough to stand by themselves. The favorable conditions mentioned seem to be especially two.

(1) Ligation of the duct must be performed within a short time after the onset of diabetes. Probably this time is not longer than a week or two; and the chance is probably better the sooner the operation is performed. If the delay is too long, it becomes impossible to check the diabetes.

(2) Preliminary and subsequent starvation are advisable. If possible, it may prove advantageous to starve the animal sugar-free before operation. But its strength should not be too far exhausted, for a period of fasting after operation is probably very important, to allow the pancreas to adjust itself to the altered conditions (perhaps to render it less susceptible to the stimulation resulting from the presence of food in the bowel).

Certain observations also suggest the possibility that duct-ligation produces its best effect when performed before the onset of diabetes. Even if effective after the onset, the improvement of tolerance is perhaps less, and the descent into Sandmeyer diabetes is more rapid, the longer the duct-ligation is delayed. This fact (if true), and the aggravation of diabetes which seems sometimes to occur when conditions are unfavorable, may perhaps receive a common explanation. The diabetes which occurs when the duct is left patent is attended by alterations of the islands of Langerhans, perhaps at first functional, later organic. The longer the duration of these degenerative processes, the less chance is there of checking the diabetes. The damaged islands are perhaps more vulnerable and more easily replaced by fibrous tissue, for in several cases in which duct-ligation has proved unsuccessful, the islands have been found apparently absent altogether; and these were the cases of maximum diabetes, in which the animal could not be starved sugar-free.

(*e*) *Application.*

The possibility of the application of these results to the therapy of human diabetes is opposed by two considerations; (1) the limits are so narrow; (2) the effect is so transient.

(1) The narrow limits have reference to the size of the pancreas-remnant. If the remnant is much more than a tenth of the gland, diabetes gravis is commonly absent even when the duct is patent. If the remnant is much less than a twentieth of the gland, diabetes gravis commonly occurs even though the duct be ligated. The difference therefore amounts to only about a twentieth of the pancreas. But if this be conceded, the matter appears in its true

light when it is observed that the functional efficiency of the existing pancreatic tissue is fully doubled. In fact, in the case of Dog 173, with a remnant which would have permitted diabetes with patent duct, diabetes was not only absent, but remained absent when half the remnant was removed. An influence which may double or more than double pancreatic efficiency is not negligible.

(2) In the case of diabetic dogs, the prevention of glycosuria by duct-ligature is only transitory. At the best, a hopeless Sandmeyer diabetes is not many months off. But here again we are dealing with only a very small mass of pancreas-tissue. When the entire pancreas is present, as in most cases of human diabetes, two possibilities are presented; (*a*) a small portion may be ligated off, and when this has finally lost its anti-diabetic power, further successive portions may be ligated similarly, and thus the effect prolonged; (*b*) the entire gland may be ligated off from the bowel at once. In dogs, diabetes has never been known to follow ligation of the ducts without removal or destruction of pancreatic tissue. Bouchardat is said [by Sauerbeck, p. 572] to have observed glycosuria on mixed diet after ligation of the ducts in dogs. It is also stated [by von Noorden (1), p. 40] that injection of the ducts with paraffin may cause glycosuria in dogs. But the fact remains that simple ligation of the ducts with avoidance of all other injury is not known to produce diabetes in dogs, though the disease might perhaps come on in the course of years.

It must be remembered that in diabetic dogs we are dealing always with an organic condition. Not only do the islets seem to undergo rapid degenerative changes, but back of that is the fact that about nine-tenths of the gland is gone forever and cannot be replaced. We are seriously handicapped from the outset, in trying to modify a primarily organic condition by means of a functional change. Any degree of success attained becomes the more striking by reason of this inherent difficulty. If the findings stated in this chapter are confirmed, they represent the first definite and unmistakeable modification of the course of pancreatic diabetes in laboratory animals. The method evidently depends somehow upon a functional modification. The fact that it may succeed in the presence of an organic condition, viz., the absence of the greater portion of the pancreas, gives some ground for hope that this functional method may prove much more successful if applied for the relief of a functional form of diabetes.

The question largely concerns the nature of the average case of human diabetes. A few cases are undoubtedly organic. The tissue-destruction is obvious, and the gross or microscopic lesions represent a condition comparable to that of the dog which has suffered surgical extirpation of nine-tenths of the gland. For such human cases, the hope is probably no greater than in dogs. But in the majority of human patients, the condition is not of this sort. Organic changes of the islands of Langerhans are in fact described for a large proportion of them; but these changes for the most part are relatively slight, and they are found in patients dead from diabetes. It would not be surprising if a primarily functional disorder of the islands of Langerhans should in the course of time lead to a certain degree of organic change in them. Autopsies of diabetic patients in the earlier and milder stages of the disease are relatively scarce. Certain it is that some diabetic glands are free from visible change, and that no pathologist can infallibly diagnose diabetes with the microscope. Various facts seem to indicate that the average case of human diabetes is functional rather than organic in origin. It remains to be seen whether clinical literature offers any hope of results from closure of the ducts in human diabetes.

B. Clinical.

It has long been a cause of wonder that diabetes is uncommon with cancer of the pancreas, even when the gland is extensively destroyed. Hansemann's idea that the tumor-cells assume the internal function does not agree with the facts; but Pearce (2), Ssobolew (3), and others have shown that the islets are generally well preserved with cancer, and thus the absence of diabetes is explainable. Halasz (1) likewise found the islets well preserved in pancreatic sarcoma. Miraille has published statistics of glycosuria in connection with pancreatic cancer; it is generally transitory, present at a certain stage, later disappearing. In other words, diabetes begins, but something causes it to cease. Cancer begins most frequently in the head of the gland. Generally either the duct of Wirsung or some of its important tributaries are occluded, the condition thus resembling the experimental ligation of the whole or part of the pancreas. Loeper and Rathery were able in some cancer cases to discover the increased blood-diastase and the other phenomena which in animals are known to follow

ligation of the ducts. Accordingly, it is advisable to give attention to this occlusion of the ducts as a possible cause of the absence or cessation of glycosuria in pancreatic carcinoma.

The association of cancer with permanent diabetes is possible; it is found in a minority of cancer cases. Bard and Pic regard such cases as representing generally an accidental complication; frequently the diabetes has plainly preceded the cancer, instead of having been caused by the cancer. Heiberg (5) indorses this view, and describes a case of his own, in which the islet-changes led him to conclude that the diabetes was independent of the cancer. Gilbert and Carnot (3) have reported a case in which diabetes apparently preceded cancer, and the cancer failed to stop the glycosuria.

Their patient was an obese woman weighing 110 kilos, who at the age of 50 noticed abnormal thirst and polyuria; a urinalysis showed 90 g. dextrose in 24 hours. Anti-diabetic diet reduced this to 18 g. in 24 hours. Notwithstanding the glycosuria, the patient remained 9 years on anti-diabetic diet in comparatively good condition. Then the digestive signs of failure of pancreatic secretion appeared. Icterus developed 2 months later and became intense. The patient lost weight very rapidly. The glycosuria was still 36 g. in 24 hours. Death occurred from rapid cachexia. The autopsy showed old fibro-fatty and cystic changes far advanced in the pancreas; to these was added a recent cancer of the head of the pancreas, with metastases in the liver. Pancreatitis was assumed as the basis of the condition.

Chauffard, discussing this case, added another, of a patient of 60, with fat-diabetes for 6 years, in whom cancer of the head of the pancreas developed with the usual symptoms and emaciation, and the glycosuria fell from an average of 50–60 g. in 24 hours to 10 g.

Similarly, diabetes sometimes exists when the pancreatic duct is occluded by stones. But as has been pointed out, especially by Opie, all such cases are easily explained by inflammatory destruction of the islands of Langerhans. Calculi frequently give rise to inter-acinar fibrosis, destroying the islets. The cancer in Gilbert and Carnot's patient was on the basis of an old pancreatitis. Such cases are essentially organic diabetes, and they agree perfectly with the findings in animals, that when a sufficiently large amount of pancreatic tissue has been destroyed, diabetes may occur whether the ducts are ligated or not. There is little therapeutic hope from ligation of the ducts in organic diabetes.

Surgical operations on the human pancreas perhaps contribute a little evidence. Naunyn (p. 119) reviews part of the literature of this subject. Extensive partial extirpations for tumor or necrosis have been followed by no immediate diabetes; after as

long as $1\frac{3}{4}$ years diabetes has been known to ensue, due to advanced sclerosis of the pancreatic remnant, as in the Sandmeyer type in dogs. Franke supposed that he had extirpated the entire carcinomatous pancreas, and the patient lived for 6 months without diabetes. The removal, however, cannot be considered as total in the strict sense; the field of operation was obscured by adhesions, and furthermore Franke states that he carefully spared a hazelnut-sized structure resembling an accessory pancreas. In contrast to the absence of glycosuria in all these cases when the pancreas-remnant, though small, was isolated from the bowel, is a case mentioned by Opie [(4), p. 110]. Here two-thirds of the normal pancreas was removed by mistake; the remaining one-third was the portion bordering the duodenum. Sugar appeared in the urine 8 hours after operation, and steadily increased during the three days that the patient lived. Possibly it would not have proved to be a permanent diabetes. In dogs, the removal of a larger fraction is necessary in order to produce diabetes; but it has already been suggested that man may be more susceptible than the dog, and that diabetes may perhaps occur with a larger pancreas-remnant, provided this communicates with the ducts. Experiments with monkeys should prove of great interest in this connection; it may not improbably be found that in them diabetes develops with larger pancreas-remnants than in dogs, provided always that the external secretion is preserved, and no non-secreting fragments left.

Gigon (1*A*) had a diabetic patient under observation in a metabolic experiment when the pancreatic duct was suddenly blocked by a stone. Digestion was impaired; but simultaneously, there was a sudden nitrogen-retention, a rapid gain in weight, and a decided improvement in the appearance, strength and well-being. Dropsy was not present, and hemoglobin-tests ruled out hydremia. The diabetes was not cured, and the D/N ratio remained practically the same. The author judges that the gain in weight was probably due to water-retention in the tissues. The case was organic diabetes. Autopsy showed long-standing atrophy of the pancreas, due to stones. Islands of Langerhans appeared diminished in number, and those present were abnormal; frequently they seemed composed of tall cylindrical epithelium apparently surrounding a lumen. Although the sections were seen by Sauerbeck, it is not impossible that some of the structures were degenerating acini. At any rate, it is of interest that in a case of

organic diabetes, when the duct was suddenly blocked by a stone in the midst of an accurate metabolism experiment, the patient's condition seemed to be temporarily improved.

Courmont and Bret described a case of pancreatic carcinoma, in which a glycosuria of 2.6 per cent came to an end as the cancer progressed. Similar cases are numerous in the literature.

Krieg reported a case as follows.

A woman, aged 67, had been constantly under the observation of a physician since 1890, because of lameness and pains in the legs due to arteriosclerosis. There were several intercurrent ailments; influenza in 1889 and 1891. On March 22, 1904, the patient went to bed on account of a severe pain in the right hypochondrium. Urine examination showed 4.2 per cent sugar by fermentation test [no record of quantity of urine, diet, etc.]. On March 30, icterus gravis began, and simultaneously the sugar disappeared from the urine. Icterus remained present under treatment with Carlsbad salts, hydrotherapy, etc.; and by April 22, pain and tenderness were definitely localized in the right hypochondrium, and a tumor was palpable there. The stools were fatty. The symptoms associated with icterus increased; enlarged liver and ascites were present. Death occurred from pneumonia on May 24. Autopsy showed a scirrhous adeno-carcinoma of the pancreas. The entire head of the pancreas was transformed into hard tumor. The bile-duct was blocked completely, and the liver full of metastases. [No statement concerning islands of Langerhans.]

Teleky reported the following two interesting cases.

The first patient was a lawyer aged 51; mother insane, one brother diabetic, two sisters hysterical, one sister with cancer of breast. In 1886 he had increase of urine, but examination apparently showed no sugar then. In May, 1887 the urine increased still more, patient grew thin and weak; in July the urine was found to contain 4.4 per cent sugar, or 50 g. in 24 hours. Strict anti-diabetic diet and a 4-weeks cure at Carlsbad reduced the sugar to small quantity but did not cause it to disappear. In September began dyspeptic symptoms, and toward the end of September a slight icterus, which increased. The feces contained no bile. The urine was heavy with bile, but sugar-free. The appearance of the patient presented nothing abnormal except the icterus. He died in delirium on November 28, and up to death the urine was constantly heavy with bile and free from sugar. Autopsy by Weichselbaum showed a small liver and very atrophic pancreas. There was chronic pancreatitis, and sclerosis of the head of the pancreas had almost closed the bile-duct, which was dilated to thumb-size. Microscopic examination disclosed merely fibrosis and atrophy; no attention was paid to islets [1887].

The second patient was a bank-clerk aged 50. Mother and one brother had gout; family history otherwise negative. In the middle of February 1901 he noticed his mouth dry; he looked badly; his weight fell in 4 weeks from 82.5 kilos to 77 kilos. The urine on March 6 was found to be 3000 cc. in 24 hours, containing 9 per cent sugar. Strict anti-diabetic diet brought the urine down to normal quantity and the sugar down to traces. The patient felt well till May 1901; then icterus with the usual attendant symptoms developed and increased; bile present in urine but absent from feces; liver enlarged but not tender. Owing to dyspepsia, the patient was

allowed to choose his own diet, and ate mostly carbohydrate, including sugar; but the urine remained sugar-free. In this condition he was at Carlsbad from June 5 to July 3. On his return, the urine was still the same; icterus the same; no glycosuria though he still ate chiefly carbohydrate, and his strength and appetite were notably improved. The feces contained fat and unchanged muscle-fibres. Operation on July 10 showed a large liver and distended gall-bladder; no gall-stones; palpable tumor in pancreas. Cholecystenterostomy was performed and the abdomen closed. Patient died July 14. Autopsy showed a nut-sized tumor in the head of the pancreas and a cherry-sized tumor in the tail. The tumors consisted of altered acinar tissue. The parenchyma of the pancreas was very fibrous; the acini had mostly disappeared. The author emphasizes the fact that cachexia, fever, or other complications cannot account for the disappearance of glycosuria in this case, for it disappeared while the patient was still in good condition and nourishing himself on a diet rich in carbohydrate.

The current explanation of cases of this type has been that glycosuria ceases because of cachexia. The same explanation regarding the influence of nephritis was discussed in Chapter XVIII. As formerly mentioned, cachexia per se always lowers, never raises the limit of sugar-assimilation. Cachexia may indeed cause cessation of glycosuria when the organism has become too weak to produce sugar, or when the ingestion of food is sufficiently diminished. But there is abundant evidence that diabetic animals and persons may reach a very low state of cachexia and still the glycosuria persist. Cachexia as an explanation of the disappearance of glycosuria in the cases under discussion fails for two reasons. (1) In organic diabetes, as in the case described by Gilbert and Carnot, cancer may supervene and the cachexia may be most intense, with jaundice and all the associated symptoms, and the glycosuria persists nevertheless. (2) In other cases, as notably in Teleky's description, glycosuria which formerly was present even on strict diet, may cease when the patient is still in relatively good condition and taking an adequate quantity of food, and remain absent although the diet contains an abundance of carbohydrate and even sugar. The patient may live for months (and in the case of nephritis for years) free from glycosuria. This is not cachexia.

The fact that the disappearance of glycosuria regularly coincides with the signs of closure of the duct, points plainly to the latter as the cause. This indication is confirmed by the results of duct-ligation in experimental animals. Two points seem to present themselves in this connection. (1) The cessation of glycosuria after the development of cancer or nephritis seems to indicate

that the diabetic disturbance in these cases was functional. If the islets had been actually destroyed or rendered organically worthless, nothing could check the diabetes. Organic diabetes is not stopped by cancer. This evidence agrees with the absolutely or relatively good preservation of the islets in the average cases, and with other known facts concerning diabetes. (2) The fact that glycosuria ceases, and carbohydrate assimilation is restored, even in patients in the more advanced stages of diabetes (glycosuria not abolished by strict diet), gives ground for hope that therapeutic results may be obtainable even in the later stages of the disease. In this respect patients seem to differ from dogs, in which results are obtainable only at the first. This difference presumably corresponds to the more rapid and more marked degeneration of the islets in dogs. It is essentially a difference between functional and organic diabetes.

It may be desirable to consider on a theoretical basis some of the possible applications of duct-therapy to human diabetes. The subject may be divided into (1) total ligation; (2) partial ligation; (3) treatment of the duodenal mucosa.

1. Total Ligation.

This is the most radical procedure. If any of the methods gives results, this preëminently should. Atrophy of the pancreas is inevitable. The resulting disturbance of digestion is amenable to treatment by pancreas-feeding. Preliminary trypsin-injections may diminish the liability to fat-necrosis, but there is a danger of death from the peculiar pancreatic cachexia, which is not negligible. It would be valuable to know why this cachexia comes on in some animals and is absent in others; is it an intoxication from chronic pancreatitis? but even if so, why the variations? In young patients, total ligation might perhaps be followed by infantilism.

Granted the disappearance of glycosuria, there is a question as to its permanency. Granted that the pancreas is organically sound and its functional disturbance overcome by the ligation, it is entirely possible that in the course of a few years the advancing sclerosis might lead to diabetes of the Sandmeyer type. There is some slight question whether the onset of this diabetes might be delayed by pancreas-feeding. Pratt and Spooner have claimed increase of tolerance from pancreas-feeding in dogs with ligated

ducts; the spontaneous irregularities of the tolerance in such animals must be borne in mind, but yet all such positive reports are valuable. In most human patients, pancreas-feeding is negative, or even increases the glycosuria; this is true whether the ducts are patent or occluded. But Wegele reported disappearance of glycosuria in a patient on pancreon treatment. E. Meyer (2) found the glycosuria diminished by pancreon in a case of pancreatic cancer. A bare possibility perhaps exists that at some stage of the condition, especially when the ducts are closed, the feeding of pancreas may benefit the carbohydrate assimilation, while at other stages it is useless or harmful. The few favorable reports which have come to my notice have all been in cases where the pancreatic ducts were closed.

If the worst is granted, viz., that any improvement following total ligation must necessarily be temporary, and that a hopeless diabetes will return in the course of months or years, the operation may still be justifiable in patients in late stages of the disease. It could not be permissible until the later stages. Surgeons are willing to extirpate the head of the gland for cancer. Franke has even advocated total extirpation. Ligation of the ducts for severe diabetes is therefore not unthinkable.

But there arises here an important question of surgical technique. In dog and man, the isolation of any portion of pancreatic tissue by any surgical procedure is regularly followed by sclerosis of this portion, and destruction of the islets by contraction of the dense fibrous tissue. The question is whether this result is unavoidable. It is possible for the human pancreas to be replaced by a loose fibro-fatty tissue, as in the case of the rabbit and guinea-pig; and in such tissue the islets remain well-preserved and there is no diabetes. S. G. Scott, for example, described a case of obstructive atrophy of the pancreas from carcinoma, in which the gland presented no very striking gross change or diminution in size. Microscopic examination showed that the parenchyma was replaced by fibro-fatty tissue, in which the islands of Langerhans were perfectly preserved; as usual under such conditions, there was no diabetes. Walker reported the case of a physician who for twenty years passed stools that were colorless and full of fat; his health was perfect otherwise, he died at the age of ninety, and autopsy showed the pancreatic duct occluded by a calculus and the gland almost wholly replaced by fat. The question therefore is, why does closure of the duct sometimes

cause the formation of dense scar-tissue, which destroys the islets by strangulation and brings on diabetes; and why does it in other cases cause the gland to be replaced by a benign fibro-fatty tissue, which preserves the islets and permits permanent health with no danger of diabetes? All that is necessary is for the surgeon to learn how to produce the latter instead of the former condition. It is imaginable that the difference may depend upon a time-element. If the duct is suddenly closed, and the highly irritating pancreatic ferments imprisoned in the gland itself, it may be that scar-tissue formation is thus produced; but if the closure takes place very slowly and gradually, the injury is less severe, and the organ perhaps becomes replaced by fatty tissue. Might the desired result be obtained by a pancreatic fistula? Escape is thus provided for the secretion, and a slow atrophy of the gland is the usual result of a fistula. Marasmus has been observed in animals from a pancreatic fistula; Bruckner and Jianu and other authors already mentioned have described even rapid cachexia and death; but it is known [Opie (4), p. 78] that with suitable diet and other precautions, an animal with a pancreatic fistula may be kept in good health even for years. In a human patient, the irritation of the skin and other inconveniences would be the most troublesome feature, but several months of annoyance (till the fistula might close) would be worth while if relief from diabetes were obtainable. At any rate, if closure of the pancreatic duct will check diabetes, it becomes purely a surgical problem to secure the replacement of the gland by fatty tissue instead of by scar tissue. There is good reason to hope that the surgery of today will be able to solve such a problem if necessary. If the gland could be replaced by fatty tissue and the islets preserved, the cure of diabetes by total ligation might be permanent, and might be in order at any stage of the disease.

2. Partial Ligation.

Fragments of the human pancreas have been known to avert diabetes for as long as $1\frac{3}{4}$ years. The possibility exists that human diabetes might sometimes be checked by ligating off a portion of the pancreas without sacrificing the rest of the gland. Here is found the possible importance of one of the questions previously discussed; viz., if an isolated pancreas-remnant of a given size is able to prevent diabetes when all the rest of the gland is removed,

will it also prevent diabetes if another remnant is also present and secreting into the bowel? Altogether, the conclusion seems warranted that the anti-diabetic action is due to changes in the pancreas, not to the exclusion of pancreatic juice from the bowel; and that an isolated fragment will be equally effective if another portion of the gland continues its external function. If the isolated portion undergoes sclerosis, it will finally lose its value, and another operation will be necessary, to ligate off another fraction of the gland. But if by establishing a fistula from the isolated portion, or by any method of slow instead of sudden isolation, it should be possible to cause the replacement of the parenchyma by fatty tissue instead of scar tissue, the isolated portion might preserve its anti-diabetic function indefinitely. Under such conditions, the method of partial ligation might prove ideal; *i.e.*, a considerable portion of the pancreas might by suitable isolation be transformed into a purely endocrine gland, while the remainder might continue to perform the digestive function. In case of a successful outcome, the patient would suffer no disturbance of health whatever.

3. Treatment of the Duodenal Mucosa.

Considerable practical importance may attach to a discovery of Lombroso (12) already mentioned. If the duodenal mucosa surrounding the opening of the pancreatic duct be destroyed with the thermocautery, the secretion gradually diminishes and finally stops altogether, though the orifice and the entire length of the duct be entirely patent. It remains to be determined what permanent results can be obtained by this method. It is well known that the mere cutting and drainage of the pancreatic duct does not produce a satisfactory pancreatic fistula; there are changes in the quantity and character of the juice, and in the gland-structure itself. But if the portion of duodenal mucosa surrounding the excretory papilla be excised and carried out to the skin, the fistula thus produced yields normal juice indefinitely. Apparently this portion of mucosa is the source of important influences affecting the pancreas. Perhaps another indication to this effect is found in the observation of Steinhaus [ref. by Rosenberger, p. 146]; a luetic ulcer which had extended from the papilla of Vater to the pancreas, was accompanied by sugar-excretion as high as 180 g. daily, with acetone. It has previously been suggested that

intestinal stimuli seem to affect the internal pancreatic function, whether directly or through the external function. Various intestinal treatments of diabetes have been proposed before now. By such cauterization or other suitable treatment, the pancreas might perhaps be rendered less susceptible to harmful stimuli; this possibility falls in line with a previous suggestion, that diabetes is an over-irritable nervous state. If by more or less extensive cautery or other destruction of the mucosa the external secretion could be permanently diminished and a partial atrophy of the gland produced, the effect might resemble that of partial ligature. Since the effect consists in an actual cessation, not a damming back, of secretion, the atrophy, if obtained, might be followed by formation of fatty tissue rather than of scar-tissue. The whole question is one which can advantageously be tested on partially depancreatized dogs.

There is much suggestiveness in the facts concerning dogs with subcutaneous grafts, as described by Minkowski and others. In the great majority of these the yield of pancreatic juice diminishes, atrophic changes occur, and the islets are preserved till destroyed by scar-tissue; diabetes meanwhile is prevented. In a small number, perhaps on account of some nervous irritation, there is hypersecretion of pancreatic juice, hyperplasia of acini and degeneration of islets; diabetes is present in full intensity. The impression is given that the same nervous state which produces functional and organic increase in the acinar tissue also produces functional and organic impairment of the islet tissue. The question is opened whether in human diabetes there may not be even an abnormally active secretion of pancreatic juice, together with a weakened function of the islets; the whole being perhaps dependent upon an irritable nervous condition, with perhaps an excessive response to secretory stimuli from the bowel. Here the facts discussed in Chapter IX find their applications; a food, such as oat-gruel, which markedly diminishes the external secretion of the pancreas (perhaps by coating the duodenal mucosa with a non-irritating slime), in many cases markedly raises the dextrose tolerance. Here also the excellent digestion in most cases of diabetes (except the organic ones) comes into notice, together with the question discussed in Chapter XVII, whether the increased hunger in diabetes is entirely secondary to the sugar-loss, or whether it is to some extent primary, due to some state of the digestive organs and their governing nervous mechan-

ism. The benefits reported by Funck and others from the intestinal treatment of certain diabetics have also been mentioned. There is ground for therapeutic hope, therefore, from measures which alter the "balance" in the pancreas, by diminishing its external and strengthening its internal function.

In closing, a brief mention may be made of organic diabetes. Though probably little amenable to treatment through any functional influence, the organic cases will probably be among those most benefited if a routine surgical treatment of diabetes is ever adopted. For by such an operation, the organic cause of the trouble would be revealed; and if undertaken early enough, the offending calculi or other cause might be removed, with the result of a permanent recovery. Cammidge has emphasized the importance of early diagnosis of pancreatic disorders, before the destruction of the gland is sufficiently far advanced to cause glycosuria. Robson makes similar recommendations. Garrod (2) mentions a case reported by Moullin, in which, with cholecystitis, there was glycosuria of 7 per cent; in operation for the removal of gall-stones, the pancreas was felt to be firm, but pancreatitis seemed absent; after operation the glycosuria progressively diminished, and the patient was discharged apparently cured. The short period of observation is insufficient to demonstrate the permanency of the cure, but in this class of cases there is good reason to expect a permanent cure. Hutcheson has reported a case with diabetic symptoms cured by gall-bladder drainage.

Conclusion.

A considerable amount of speculation has been unavoidable in this chapter. Like all such, it may prove fallacious. The suggestion to treat human diabetes by duct-ligation or some modification thereof probably will be, and properly should be, received with much skepticism. There is one central question in this whole matter. Is it a fact that under certain definite conditions, diabetes occurs in dogs when the pancreatic duct is patent and remains absent when the duct is closed? The conditions in question are the removal of approximately nine-tenths of the pancreas, without injury of blood-vessels or any other structures. If the above difference is not produced by duct-ligation, then my results are atypical, and I shall have to regret that my series was not long enough to prove them atypical. But if duct-ligation does pro-

duce the difference described, no apology is necessary for the theoretical deductions and therapeutic suggestions here offered. This result of experimental duct-ligation seems to accord very well with certain facts reported in clinical literature. Granting that these relations are correct, the therapeutic value of the suggested procedure is obviously still not to be positively predicted. If diabetes is a functional disease, it is very likely of central nervous origin; and the cure of a central nervous condition by a peripheral operation is to some extent improbable. But whether it is a permanent cure or not, the procedure may perhaps at least be of value as a palliative measure. If successful at all, some such procedure may possibly be found of value also in certain cases of pathological obesity.

Any one with operative facilities can test the alleged effects of duct-ligation within a very few weeks. If the findings are confirmatory of mine, the matter then perhaps becomes worthy of clinical notice. It has appeared to be my duty to bring out the favorable possibilities as strongly as possible. The unfavorable aspects should also be given due consideration. A very conservative and critical judgment of every detail is to be hoped for, and no step should be taken except on the basis of full experimental investigation. The contents of this chapter are aimed only to stimulate research, not an immediate therapeutic application. Therapeutic recommendations, if made, must come from others, and must be based upon harmonious experimental findings of a number of independent investigators.

CHAPTER XXIII.

SUMMARY.

THE investigation has been a unified whole. Essentially, it has consisted of two lines of study, (1) the behavior of sugars in the body, (2) the production and modification of diabetes. These two have been joined through the important question of the influence of sugar in producing diabetes or its complications. An intertwining of the two themes has been inevitable; for example, in studying the behavior of sugars it was necessary to compare non-diabetic and diabetic animals, and to describe how the diabetes was produced; and in the different forms of glycosuria studied, it was advisable to combine in the same chapter the behavior of sugar under the given glycosuric conditions, and also the possible influence of those conditions in producing diabetes. The numerous tempting side-lines have been avoided as far as possible; a very few have been followed a short distance either unintentionally, or for the sake of some view-point which they might possibly afford for the study of diabetes. Now in retrospect, it is possible to separate the two themes somewhat, to point out relations more clearly, and to state more distinctly the results and conclusions derived from the research as a whole.

1. BEHAVIOR OF SUGARS IN THE BODY.

The principal conclusions may be summarized as concerning (A) general tolerance, (B) toxicity, (C) paradoxical law, (D) diuretic action, (E) clinical tests of diabetes.

A. GENERAL TOLERANCE.

The question of sugar-tolerance was studied with respect to (I) different animal species, (II) different sugars and other carbohydrates, (III) different conditions modifying tolerance, and (IV) different methods of testing tolerance.

I. Different animal species differ widely in sugar-tolerance. There is no fixed relation to position in the animal scale, develop-

ment of the islands of Langerhans, food or other habits, or other known conditions.

II. Different sugars and other carbohydrates differ widely in assimilability, especially on parenteral introduction. Nearly all are utilized in very appreciable proportion. The most striking exception is lactose, the limit of assimilation of which is very low. It is probable that accurate tests will show that lactose parenterally introduced is utilized in measurable amount, and that no normal animal exhibits toward any sugar that total inability of utilization which the totally diabetic animal exhibits toward dextrose. The question of diastases arose in connection with certain injections; it was concluded that the blood-diastase probably has no normal existence as such, and the existence and function of diastases and other enzymes in living organs are open to question. It remains theoretically probable that enzymes are produced and made use of inside the living cell, but the enzyme-content of dead cells is in any event not a measure of the enzymic activity of the living cells. Observations of the diastatic activity of dead organs or tissues, either singly, or in combination as by the Cohnheim method, possess no significance for the study of diabetes.

III. For details concerning influences modifying tolerance, reference may be made to Chapter I. In other chapters, the effects of starvation and various toxic and nervous conditions upon the tolerance have been studied. The "hunger-glycosuria" of dogs was verified. It is less notable in other species (fasting cats, guinea-pigs). The general effect of cachexia is to lower tolerance. A raising of tolerance by cachexia, as alleged for human diabetes under certain conditions, is contrary to experimental evidence.

IV. Tests of sugar-tolerance may be oral, subcutaneous, or intravenous. Each may possess some advantages. The oral method holds its clinical position by reason of its convenience; it is open to error through irregularities of absorption (delayed absorption perhaps important in myxœdema and acromegaly), and the rôle of the liver is important, especially in the case of levulose. The intravenous test is perhaps the least useful; it is merely a kind of saturation-limit, representing the amount of sugar the tissues and fluids can hold without overflowing the kidneys; undue importance may thus attach to slight variations of renal permeability; especially, the test does not determine the

ability of the tissues to withdraw sugar from the blood. The subcutaneous method is the best test of the power of the body-tissues to utilize sugar. Irregularities of absorption are minimal; the liver-path is avoided; and the actual efficiency of the tissues in burning or storing the injected sugar is determined. The subcutaneous test proves clearly that every important reduction of pancreatic tissue correspondingly reduces the dextrose-tolerance; other tests have permitted confusion on this point. The relations are brought out plainly in the case of levulose. The oral tolerance of levulose is not much less than that of dextrose, because the liver stops nearly all the levulose. The intravenous tolerance of levulose is approximately the same as that of dextrose, for the value represents a mere immediate saturation-limit. The subcutaneous tolerance of levulose is a very small fraction of that of dextrose, because this method tests the power of the general tissues to utilize levulose, and this power is easily exceeded. Accordingly, if it is desired to rule out every possible irregularity of absorption and test the simple saturation-limit, the intravenous method may be useful. For clinical convenience, and especially for the levulose-test of hepatic function, the oral method is useful. For laboratory convenience, for minimal variations of absorption, and for a test of the rate at which the tissues utilize sugar, the subcutaneous is the method of choice. For most purposes, the rate of utilization of sugar by the tissues is the important thing to be determined.

B. Toxicity.

Notions concerning the toxicity of sugar have been experimentally refuted.

I. *Diabetes and Complications.* — (*a*) Neither diabetes nor any of its complications can be produced in normal or predisposed animals by prolonged excess of dextrose. This was seen especially in the case of Cat 15, in which prolonged dextrose injections resulted in functional nervous disorder, increased dextrose tolerance, and possible alterations in the chromaffin and sexual organs. The elevation of tolerance was due to lessened renal permeability rather than to increased rate of utilization. Idiosyncrasy may be a factor in the nervous phenomena, for a certain number of cats subjected to starvation plus dextrose injections develop a state of ataxia, while the majority do not. Certain conditions produced by single excessive doses of sugar—albuminuria, lowered resistance

to infection, nervous symptoms — are no more due to a specific action of sugar than is the so-called "cataract" produced by similar means. The sudden disturbance of molecular equilibrium is the efficient agent, and similar effects can be produced by substances other than sugar.

(*b*) The harmlessness of dextrose is especially demonstrated in suitable diabetic animals, whether with diabetes gravis or diabetes levis. In the former case on meat diet, in the latter case on carbohydrate diet, the hyperglycemia and glycosuria may be equal or superior to that of average totally depancreatized dogs. The complications attending total pancreatectomy are absent. In particular, the resistance to infection and the healing of wounds are satisfactory. These complications therefore are independent of the sugar-content of the tissues and fluids, and even of the ability of the tissues to utilize dextrose; they are due to the loss of other internal functions of the pancreas.

II. *Young Animals.* — Sugar is without specific toxicity in young animals. The evidence as far as it goes indicates that they bear sugar even better than adult animals. A well-marked increase in weight is obtainable from dextrose injections, and there is a possibility that suitable injections actually spare nitrogen.

III. *Nitrogenous Balance.* — In adult animals, sugars administered parenterally do not spare nitrogen. On the other hand, they produce no increased nitrogen loss if given in suitably small doses. The behavior in normal is in striking contrast to that in diabetic animals, in which dextrose injections produce a sudden and pronounced increase of nitrogen excretion.

IV. *Fat.* — Continued artificial hyperglycemia does not cause increase of weight in adult animals. The assumption that obesity may result from fat-storage due to hyperglycemia in incipient diabetes lacks experimental foundation. The underlying idea, that fat-cells retain the power to utilize sugar while other cells are losing this power, is likewise a pure assumption. It is made improbable by the evidence showing that diabetes is due to lack of an amboceptor substance, which renders dextrose less available to all the tissues. Other evidence indicates that the pancreas has a specific function in the fat-economy. It is preferable to explain pathological obesity as a disease of the pancreas, or sometimes of other organs of internal secretion. Obesity and diabetes may then be related as two disturbances of the same organ or system.

V. *General well-being.* Doses of sugar disturb the general well-being only when large enough to produce molecular damage. Small daily dextrose injections do not prolong, and may shorten slightly, the life of fasting animals. The same is true not only of injections of other substances, but probably also of the feeding of any non-nitrogenous energy-bearers. On the other hand, in conditions of extreme weakness, a limited number of small dextrose injections may prove highly strengthening and beneficial. As test-objects for crucial determination of the effects of dextrose, cats starved to the verge of death were chosen. In these animals it was found that dextrose injected subcutaneously is not a toxic substance, but on the contrary is a valuable food and stimulant. Injected dextrose possesses no advantages over dextrose by mouth, except ready absorption and avoidance of the intestinal tract. Dextrose injections are to be recommended as a therapeutic measure in a certain limited class of cases. In other cases sugar feeding should be of value.

C. Paradoxical Law.

Briefly, this law is that the more sugar is given, the more is utilized. Limits of tolerance in non-diabetic animals are all apparent, not real; there is no real limit of the power of utilization of sugar, except death. The law applies to all species of animals, to all methods of administering sugar, and to all sugars and carbohydrates, provided they can be utilized at all. If lactose is utilizable at all, this law will presumably apply to it. Different sugars may obey the law in different degree. For example, the apparent tolerance of maltose is higher than that of levulose, since larger injections of the former than of the latter are assimilated without mellituria. But as the doses are increased, the real tolerance of levulose is found to be high, and the mellituria from maltose soon becomes far greater than that from levulose.

The paradoxical law of dextrose distinguishes sharply between diabetic animals and every type of non-diabetic animals. The limits of tolerance in diabetic animals are real and not apparent. In totally diabetic animals, an injection of dextrose causes an increment of glycosuria not only equal to, but frequently greater than, the injected dose. In milder diabetes, not only is the proportion of excreted to injected dextrose generally high, but the assimilation may be made worse instead of better by over-doses —

just the opposite of the paradoxical law. On the basis of this law, distinctions have been drawn experimentally between diabetes and the following forms of glycosuria.

I. *Alimentary Glycosuria.*

II. *Hunger Glycosuria.* — Inanition lowers the apparent tolerance, but leaves the real tolerance unchanged.

III. *Toxic Glycosuria.*

IV. *Phloridzin Glycosuria.*—A given dose of phloridzin poisons within definite limits. Even with the so-called "maximum" poisoning, it is only necessary to increase the dosage of sugar sufficiently to find that the power of sugar-utilization is still present. The increase of utilization with increase of dosage is strictly in accord with the paradoxical law.

V. *Adrenalin Glycosuria.* — Much of an injected dose of dextrose may be utilized at the height of adrenalin glycosuria, and the utilization increases with increase of dose. The dextrose paradox is useful evidence in showing that adrenalin glycosuria is not a diabetes, and does not depend upon inhibition of the pancreas, nor upon neutralization, destruction or insufficiency of the internal pancreatic secretion.

VI. *Thyroid Glycosuria.* — The above statements apply.

VII. *Nervous Glycosuria.* — The paradoxical law is applicable to piqûre glycosuria, emotional glycosuria, and presumably other forms. It is valuable in furnishing a sharp distinction between true diabetes and simple nervous glycosuria.

The retained power to utilize dextrose, in amounts increasing with the dose, is characteristic of every non-diabetic form of glycosuria. There may be a considerable apparent diminution of tolerance, as in cachectic states; but the paradoxical law still holds. There may be an over-production of sugar in the liver, as in many forms of glycosuria. There may be a condition of intoxication, as after injection of various harmful substances. There may be an increased renal permeability, as after certain diuretics or renal poisons. There may be a circulation of sugar in abnormal combination, as probably in phloridzin poisoning. There may be an excess of other glandular secretions, as of the adrenal or thyroid. There may be nervous influences, which act not only upon the liver to cause excessive production of sugar, but at the same time upon the kidneys to cause diuresis and abnormally active elimination of sugar (as in piqûre and some other nervous glycosurias). The dextrose paradox distinguishes all

these conditions from diabetes. It proves that diabetes is not a lowering of tolerance comparable to other conditions of lowered tolerance: that it is not a simple over-production of sugar, nor an alteration of renal permeability, nor an over-action of certain glands, nor a state of the nervous system *per se*, nor any of the other conditions mentioned. Perhaps its greatest value lies in demonstrating that diabetes is not a simple over-production of sugar. The paradoxical law furnishes one of the two tests which set apart diabetes as a condition *sui generis*.

D. Diuretic Action.

The observation of numerous investigators, that all the common sugars are diuretics when given intravenously, was verified. But all the freely utilizable sugars, when given otherwise than intravenously (orally, subcutaneously, intraperitoneally; also, according to Halasz, rectally) are anti-diuretics; *i.e.*, they diminish the output of urine. In other words, as respects diuresis, these sugars when given intravenously obey the law of crystalloids, and when given otherwise obey the law of colloids. Even with the less assimilable sugars (lactose, saccharose) the diuretic action is absent or insignificant after subcutaneous administration. In this respect the sugars differ radically from salts and other diuretics, which have a rather similar diuretic action by all modes of administration, when allowance is made for the rate of absorption. In diabetes this difference is abolished as respects dextrose, and dextrose comes to obey the diuretic laws of a salt; *i.e.*, its diuretic activity is similar, when it is given intravenously, orally, subcutaneously, or otherwise. On the basis of this diuretic test, diabetes was distinguished experimentally from the following forms of glycosuria.

I. *Alimentary Glycosuria.* — Dextrose invariably diminishes the urine. Also the rule is, the more sugar the less urine.

II. *Hunger Glycosuria.* — Especially in dogs, starvation may reduce the tolerance very low, so that relatively small doses of dextrose may produce considerable percentages of glycosuria. Dextrose remains a marked anti-diuretic.

III. *Toxic Glycosuria.* — The glycosuria following the injection of various harmful substances is generally accompanied by oliguria, unless the substances themselves happen to be diuretics.

In either event, a dose of dextrose simultaneously increases the glycosuria and diminishes the diuresis.

IV. *Phloridzin Glycosuria.* — In phloridzin poisoning, glycosuria and polyuria are not parallel. My experiments have shown higher percentages of sugar in the smaller specimens of urine. But without going into the disputed question of the primary or secondary diuresis of phloridzin, the essential fact here is that in phloridzin poisoning dextrose retains its usual behavior; *i.e.*, it is a diuretic when given intravenously and an anti-diuretic when given orally or subcutaneously, even though the glycosuria is considerably increased.

V. *Adrenalin Glycosuria.* — Adrenalin given subcutaneously is a diuretic, therefore polyuria accompanies the glycosuria. But the tendency of injected dextrose is still to diminish the urine; it is not a diuretic, though the glycosuria may be raised very high.

VI. *Thyroid Glycosuria.* — In the glycosuria produced by thyroid feeding, dextrose retains its usual properties.

VII. *Nervous Glycosuria.* — Here again, the nervous influence may cause a tendency of polyuria to persist when dextrose is given. It is well known that polyuria is not dependent upon glycosuria, for nervous polyuria may occur just as readily (from emotion, piqûre, or other stimuli) alone as in company with glycosuria. The anti-diuretic action of oral or subcutaneous doses of dextrose is still demonstrable. The glycosuria may thereby be raised to the level of the highest diabetic percentages, but a diuretic action of dextrose, as in diabetes, is never obtainable.

This test also contributes evidence concerning the nature of diabetes. Diabetes is not a lowering of tolerance comparable to other states of lowered tolerance; it is not a simple over-production of sugar; it is not an alteration of renal permeability; it is not an over-action of alleged "diabetogenic" organs; it is not a state of the nervous system *per se*, nor any combination of the above conditions. Inanition or various toxins may lower tolerance, but they never make dextrose a diuretic. Phloridzin may withdraw dextrose from utilization and compel its elimination, presumably by binding it in an abnormal combination; but it cannot make dextrose a diuretic. Nervous influences or drugs may cause over-production of sugar in the liver and at the same time cause diuresis and abnormally active elimination of sugar through the kidneys; but they never make dextrose a diuretic.

One of the most valuable points of this test is its proof that diabetes is not a simple over-production of sugar; for the simple over-production of dextrose cannot cause orally or subcutaneously administered dextrose to act as a diuretic.

The explanation proposed for these phenomena is that dextrose exists in the normal body in a state of colloid combination; as a colloid it can be utilized by the tissues, and it diminishes diuresis like other colloids. It assumes the colloid form in passing through any living membrane; it never circulates in crystalloid form in the normal organism except for a certain length of time after direct intravenous injection. In the diabetic organism, dextrose circulates as a free or very poorly combined crystalloid; in this state it is not available to the tissues, and it is a diuretic like other crystalloids. Other sugars are presumably combined with varying degrees of firmness in the body; the firmness or looseness of such combination may perhaps be one of the factors governing the relative ease with which different sugars are utilized. Maltose has greater tendency to diminish urine than saccharose or lactose; dextrose and levulose diminish it more than galactose. All sugars are probably combined in some degree; even lactose, when injected subcutaneously, frequently fails to increase the urine unless increased drinking is permitted, and the urine-specimens with the highest lactose percentages may be the smallest in volume. The contrast between intravenous and subcutaneous injection is always great in non-diabetic animals. Neither lactose nor any other sugar has, in non-diabetic animals, that consistent diuretic effect, irrespective of the mode of introduction, which salts and most other diuretics have, and which dextrose has in diabetic animals.

Hypotheses Rejected.

The hypothesis of the combined state of dextrose in the normal organism has been chosen in preference to other conceivable hypotheses to explain the phenomena observed. The other interpretations considered, and the reasons for rejecting them, are as follows.

(a) It might be assumed that a special state of the **nervous system** exists in diabetes, consisting in a specific sensitiveness to dextrose, the response taking the form of a polyuria of nervous origin. But known states of nervous glycosuria and polyuria (especially piqûre) display no such sensitiveness to dextrose, and in diabetes no such sensitiveness exists toward other sugars. The

above assumption requires no serious consideration until there is something to support it.

(b) **Slow absorption of the sugar**, when introduced otherwise than intravenously, may be urged as an explanation of the absence of diuresis. But there may be rapid peritoneal absorption, with the usual oliguria. In any event, the time-element is not a factor. The reason why NaCl is a diuretic and dextrose an anti-diuretic when they are given orally or subcutaneously, is not merely that the former is more rapidly absorbed; for when all necessary time is allowed, and when the absorption has resulted in intense hyperglycemia and glycosuria, the urine is diminished instead of increased. The greater the hyperglycemia and glycosuria, the smaller the quantity of urine — just the reverse of the rule after intravenous injection. Furthermore, the rate of absorption of dextrose in diabetes is not known to differ from the rate in non-diabetes, yet dextrose is a powerful diuretic in diabetes when given orally or subcutaneously; here it actually behaves like a salt, the diuresis from oral or subcutaneous being similar to that from intravenous introduction, with allowance of the necessary time for absorption.

(c) **Osmotic effects** may seem to offer a plausible explanation. These may be considered as (1) general and (2) local.

(1) *General osmotic effects* from large sugar-injections may result in general weakness, circulatory changes, and alterations in the kidneys. The absence of diuresis might be supposed to be due to these causes. This possibility was ruled out in Chapter VI, the principal considerations being: —

(α) Large doses of salts, urea, etc., may produce these general osmotic effects, but are diuretics nevertheless.

(β) Equi-molecular doses of different sugars (dextrose, lactose, etc.) produce similar effects of prostration, etc., but widely different diuretic effects.

(γ) These general osmotic effects of dextrose are similar in diabetic and in non-diabetic animals, but the diuretic effects are opposite.

(2) *Local osmotic effects* result in a considerable accumulation of liquid at the site of subcutaneous injection, or in liquid diarrhea when large doses of sugar are fed. This local accumulation may be supposed to diminish diuresis by withdrawing a portion of the available water. That this explanation is not adequate is shown as follows:

(α) Local accumulation of liquid after subcutaneous injection of dextrose in diabetic animals resembles that in non-diabetic animals, yet dextrose is an active diuretic under these conditions in diabetic animals.

(β) Strong sodium chloride solutions also produce great local œdema, but the diuretic effect is obtained nevertheless.

(γ) Equimolecular doses of different sugars produce similar local œdema but widely different diuresis.

(δ) Information is obtained by taking advantage of the peculiarities of levulose. Levulose resembles dextrose in physical properties, and in its diuretic activity when given intravenously. When given subcutaneously, small doses cause the excretion of relatively high percentages in the urine. The result is a maximum of sugar in the urine with a minimum of local œdema. Under these conditions, levulose exhibits an anti-diuretic property as marked as that of dextrose. The diminution of urine with high mellituria is seen when the dog is not thirsty, *i.e.*, when there can be no very pronounced drying of the tissues.

(ϵ) Partially depancreatized, non-diabetic animals are serviceable for tests with dextrose. The tolerance may be brought very low, so that with minimum dosage and with minimum local œdema the glycosuria is relatively high. Under these conditions, and with a full supply of drinking water, dextrose is still an anti-diuretic.

All the above results are in striking contrast with those following intravenous injection of dextrose in any animal, or introduction by any channel in diabetic animals. In these cases dextrose produces pronounced diuresis, even when a considerable drying of the tissues is involved in the process.

(d) **Higher percentages in diabetes.** It may be imagined that dextrose is a diuretic in diabetic animals because not utilizable, so that higher percentages result in blood and urine than in normal animals. This explanation is inadequate for the following reasons.

(1). It does not explain why dextrose should diminish the urine in non-diabetic animals.

(2). After suitable dextrose injections, analysis shows high percentages of sugar in blood and urine, certainly high enough to produce intense polyuria in diabetic animals. Absence of diuresis is therefore not due to lack of sufficiently high dextrose-percentages in blood or urine.

(3). The above-mentioned facts regarding levulose in normal animals and dextrose in partially depancreatized non-diabetic

animals apply here. Since the excess of sugar in blood and urine is so easily produced, there should at least be some demonstrable tendency toward diuresis, if the sugar is a diuretic. But the anti-diuretic effect is well marked.

(4). The effects of different sugars may be compared. For example, lactose is almost as inutilizable in normal animals as dextrose is in diabetic animals. Each must be excreted in practically quantitative manner. When given intravenously in equi-molecular doses, their diuretic action is so nearly alike that investigators have disputed as to which is the more active. When given subcutaneously, a somewhat similar comparison should be possible, allowing perhaps a little longer time for absorption of the lactose. But lactose injected subcutaneously in a non-diabetic animal does not produce the active diuresis which dextrose produces in a diabetic animal. Also, in the diabetic animal, lactose does not produce diuresis like dextrose, but on the contrary retains the same behavior which it shows in non-diabetic animals.

(5) Certain non-diabetic glycosurias (phloridzin, adrenalin, piqûre, etc.) may show heavy sugar-excretion. Oral or subcutaneous introduction of sugar may then cause the most intense hyperglyceima and glycosuria, equal to anything ordinarily seen in diabetes, and a large proportion of the administered dextrose may be excreted. But a diuretic action of dextrose, as found in diabetes, is never obtained.

(e) **Differences in the cells instead of in the sugar.** The position might be taken that the internal secretion of the pancreas acts upon the cells rather than upon the sugar; that the sugar circulates free; but the internal pancreatic secretion enables the body-cells to use this free sugar, and enables the renal cells to hold back the free sugar. Figuratively, the pancreatic secretion may be imagined to produce in the kidney a semi-permeable instead of a permeable membrane. But when dextrose in its own crystalloid form is injected directly into the circulation, it runs through the renal filter just as easily as in diabetes, and with the same diuretic effect. That is, the normal kidney does not hold back free sugar any more efficiently than the diabetic kidney; the difference is in the sugar, not in the kidney.

Various theoretical considerations in connection with the hypothesis of combined sugar have been discussed, especially in Chap-

ter VII. It has been suggested as a probability that combinations exist for nitrogenous foodstuffs, and as a possibility that they exist to some extent for inorganic substances. Diabetes insipidus and other disorders have been mentioned in this connection. But the most valuable complement to the evidence furnished by sugar is the evidence furnished by fat. The change in sugar is physiologically demonstrable; the change in fat is chemically and microscopically demonstrable. The fat-droplets disappear; the fat becomes a colloid, soluble in water, insoluble in ether, responding to none of the ordinary tests for fat. Presumably crystalloid and fat alike are unavailable to the cell as such, but both alike are anchored and absorbed by the cell as colloid.

The conclusion therefore has been that the sugar of the normal body is combined with some substance in colloid form, which makes it available to the tissues. The combining substance has been spoken of as an amboceptor. Since dextrose occurs free when the pancreas is absent or insufficient, it is assumed that the combining substance is furnished by the pancreas; the term pancreatic amboceptor has been used as synonymous with the internal secretion of the pancreas. Diabetes has been defined as deficiency of pancreatic amboceptor.

E. Clinical Tests of Diabetes.

The paradoxical law and the diuretic action of dextrose may be found of some service for clinical tests of diabetes. They are probably more specific for decision between active diabetes and other forms of glycosuria which may imitate it, than for detecting incipient diabetes in its earliest stages. The uses and limitations of the tests were discussed in Chapter VII.

2. THE PRODUCTION AND MODIFICATION OF DIABETES.

The literature contains confused and misleading statements to the effect that diabetes may result when $\frac{1}{6}$–$\frac{1}{12}$ of the pancreas is left in position; while on the other hand Minkowski found diabetes prevented by $\frac{1}{15}$ of the pancreas, Harley by $\frac{1}{20}$ of the pancreas, and other authors by tiny shreds unintentionally left at operation. Undue mystery and perplexity have thus been thrown about the pancreas and about diabetes. The confusion is due to two causes:

First, the failure to distinguish between transient and permanent diabetes, and especially between immediate and Sandmeyer diabetes. For example, there is no such thing as an immediate and lasting diabetes when one-sixth of the pancreas with adequate blood-supply is left in position. Removal of five-sixths of the pancreas may sometimes be followed by a transient glycosuria; also, if the remnant is isolated from the bowel, it will atrophy, and when this atrophy is sufficiently far advanced a permanent and fatal diabetes of the Sandmeyer type will develop. There are no exceptions to this rule, unless glycosuria happens to be suppressed by cachexia.

Second, the early questions concerning the influence of the pancreatic juice caused the earlier investigators to ligate the pancreatic ducts or make subcutaneous grafts. Later workers have followed these methods for no satisfactory reasons. Important confusing factors are thus introduced. Generally speaking, Minkowski, Harley and others are fully correct in the statement that very small remnants of isolated pancreatic tissue, provided the circulation is uninjured, suffice to prevent diabetes until atrophy occurs. Diabetes does not occur when $\frac{1}{6}$–$\frac{1}{12}$ of the pancreas is left in position with circulation intact and with ducts ligated; exceptions apply only to transient post-operative glycosuria, or to a subsequent Sandmeyer diabetes. For various known and unknown reasons, the nutrition and preservation of a pancreas-remnant with ligated ducts are subject to wide variations, and these explain the widely different findings of different investigators by this method.

When all complications, especially interference with the excretory channels, are avoided, a regular and orderly sequence of experimental cause and effect is obtained, and the unnecessary mystery is stripped from the subject. The normal pancreas is necessary for normal carbohydrate metabolism. Every important reduction of pancreatic tissue is followed by a corresponding reduction of the dextrose tolerance. With progressive reduction, the approach to the diabetic condition is closer and closer, till finally transient or milder forms of diabetes are produced, and then the more severe forms. Total pancreatectomy is not necessary for uniformly positive results, and the conditions obtained are a satisfactory imitation of the human disease. The subject may be considered on the following plan.

A. Diabetes by pancreatic operation.
B. Modifying influences.
  I. Influences yielding negative results.
  II. Influences yielding positive results.
    (*a*) Toward producing diabetes.
    (*b*) Toward preventing diabetes.

A. Diabetes by Pancreatic Operation.

I. Diabetes gravis .... (*a*) Permanent. (*b*) Transient.
II. Diabetes levis..... (*a*) Permanent. (*b*) Transient.

Diabetes gravis is the condition in which dextrose is excreted on meat diet. It results regularly from the uncomplicated removal of nine-tenths of the pancreas. It sometimes results when larger remnants are left, but with the larger remnants the condition is sometimes transient, passing over into permanent diabetes levis. Careful estimates at operation, not postmortem weighing, must generally determine the size of remnants, because of changes due to inflammation, fibrosis, and true hypertrophy.

Diabetes levis is the condition in which dextrose is excreted on starchy diet but not on meat diet. It results when an eighth or sometimes a seventh of the pancreas is left in position. When a sixth of the pancreas is left, there may in some cases be diabetes levis, but it is transient.

The above classification is for purposes of convenience, and a distinction must be made between absolute and relative terms. Permanent diabetes gravis is an absolute term; by starvation or cachexia sugar-freedom may sometimes be produced, but there is no recovery, and death is the regular outcome. Transient diabetes levis is an absolute term; the glycosuria ceases, generally (perhaps only) after anatomic hypertrophy of the pancreas-remnant; there remains throughout life a tendency to easy alimentary glycosuria, but no true diabetes and no condition incompatible with permanent well-being. The two intermediate terms, transient diabetes gravis and permanent diabetes levis, are relative. The former condition passes into the latter. The latter may continue, even for months, glycosuria being present on starchy diet and absent on meat diet. But the condition is genuine though mild diabetes; and a sufficiently long continuance

of a diet which causes glycosuria produces, as in human diabetes, an aggravation of the disease, so that sugar is finally excreted on meat diet, and the end-result is permanent fatal diabetes gravis.

Acetonuria is regularly present in the later stages of this type of diabetes, with the typical sweet diabetic odor. The ferric chloride test has been negative throughout my experience. Tests for β-oxybutyric acid have not been made.

In this type of diabetes, the islands of Langerhans in the pancreatic remnant at first show no positive alterations. In certain early cases, especially with hypertrophy of the remnant in transient diabetes, appearances of hyperplasia of the islets have been observed. After a longer continuance of diabetes, changes in the islets have been found, which apparently are constant and specific, viz., diminution in the number of cells, and degenerative changes in those that remain, in the form of deficiency of cytoplasm, pyknotic nuclei, and occasional naked nuclei. The islets may then diminish in number and later apparently disappear altogether. The acinar tissue does not participate in these changes. Non-diabetic animals have been subjected to a variety of experimental conditions, but have never shown the above-mentioned diabetic changes in the pancreas. Absence of islets has never been observed in non-diabetic animals except in connection with general changes such as might well obscure islet-cells even if present. Convincing evidence of transitions between acini and islets has not been found in diabetic or non-diabetic animals, and the conclusion is against such a process. The observations are interpreted in favor of the insular hypothesis of diabetes, but at the same time an internal function of the acinar tissue is considered probable.

B. Modifying Influences.

By avoidance of complications, the diabetic effect of pancreatic operations comes down to a fixed rule. By removal of a suitable proportion of the pancreas, it is possible to bring an animal close to the verge of diabetes, yet to know with certainty that the animal will never of itself become diabetic. The line may be drawn so closely that the removal of a fraction of a gram of additional pancreatic tissue may make the animal diabetic. Such animals therefore constitute reliable test-objects for judging the effects of various agencies with respect to diabetes. If any agency

has any important tendency to produce diabetes, its influence should surely be equal to the removal of a fraction of a gram of pancreatic tissue. Therefore, in an animal predisposed by suitable operation, the influence in question can be tested. Also, if any agency has any important influence in preventing or curing diabetes, its influence should be able to counteract the removal of a fraction of a gram of pancreatic tissue. Accordingly, if an animal is first predisposed without being made actually diabetic, and later is made diabetic by removal of a trifle of pancreatic tissue, it is possible to judge whether the anti-diabetic agent in question is able to neutralize the effect of the removal of this trifle of pancreatic tissue, and thus abolish or modify the diabetes. In actual practice, the lines are not necessarily drawn so closely as this. Certain agencies exist, of which the influence, in one direction or the other, is equivalent even to several grams of pancreatic tissue. Leeway is also afforded by the knowledge that transient diabetic conditions exist; therefore, if a given agency in a predisposed animal is unable to produce or prevent diabetes permanently, it may at least be expected to produce some temporary effect.

I. Influences yielding negative results were as follows:

(*a*) Alimentary glycosuria. If an animal is not diabetic, even though predisposed, it can apparently never be made diabetic by any amount of sugar feeding or injections. Sugar can aggravate an existing diabetes. It may perhaps sometimes render permanent a diabetes which otherwise might prove transient. But sugar possesses no power to make a non-diabetic animal diabetic. This evidence has an application to the incidence of human diabetes. The increased incidence of diabetes among races and classes who consume much sugar is not due to any production of diabetes by sugar, but to the bringing out of existing diabetic tendencies by sugar, when without sugar the disease would be postponed to later life, or in some persons would remain latent altogether. Sugar may thus be assigned a place in connection with the incidence of diabetes, but the importance of other (especially nervous) influences affecting the same class of people should not be underestimated.

(*b*) Acid intoxication and related influences are without diabetogenous effect. There is no evidence that diabetes is a primary acidosis.

(*c*) Various agents producing toxic glycosuria show no tendency to produce diabetes in predisposed animals.

(*d*) Phloridzin poisoning is without relation to diabetes and has no essential influence one way or the other. Phloridzin glycosuria is presumably due to the presence of some abnormal compound from which the kidney splits off sugar. The mellituria from glycogen, dextrin, or (in dogs) cane-sugar may furnish a possible analogy.

(*e*) Adrenalin glycosuria is without relation to diabetes. The same is true of the glycosuria following thyroid feeding, and of the combination of this with adrenalin. As the excess of these substances fails to produce diabetes even in predisposed animals, so also the operative reduction of adrenal or thyroid tissue, or both, has failed to check or modify an existing diabetes. In the latter type of experiments it may be necessary to distinguish between a genuine cure of diabetes and a mere suppression of glycosuria by cachexia. The polyglandular doctrine of diabetes is without foundation. It is still possible that there may exist cases of chronic glycosuria not of pancreatic origin nor due to deficiency of amboceptor, and therefore not diabetic.

(*f*) Certain nervous injuries have shown no diabetogenous influence in predisposed animals. Among them may be mentioned operative traumatism of the pancreas-remnant and its neighborhood, breaking of the nerves to the remnant or in the hepatic or other plexuses, local or general infections about the pancreas-remnant or elsewhere, temporary mechanical vagus stimulation, and irritation of a semilunar ganglion by means of a ligature with ends protruding externally. It is considered that transient and paralytic injuries are of negative promise, but that the possible effect of various chronic irritative lesions constitutes a valuable field of research.

(*g*) Certain circulatory alterations have shown no diabetogenous influence in predisposed animals.

(1) One of these is the ligation of as many vessels as possible without producing necrosis of the pancreas-remnant. Partial ligation in this manner has a diabetogenous influence only in the Sandmeyer procedure, when the duct is ligated; not when the duct is left patent and atrophy thus prevented.

(2) Another negative procedure is the obliteration of the portal vein, provided it is done slowly enough. When the portal vein is surrounded by a small ligature, untied, with the ends protruding

outside the abdomen, the vein may be gradually obliterated without perceptible clinical result. When a massive ligature (*e.g.*, picture-wire) is similarly used, a condition resembling diabetes insipidus has been observed. This condition is perhaps due to a circulatory disorder of the pancreas, and may perhaps indicate that diabetes insipidus is a disease of the pancreas. But in this condition, the islands of Langerhans retain normal appearance, the carbohydrate tolerance is apparently not lowered, and true diabetes is not produced in a predisposed animal. Therefore, even if it be a disorder of the pancreas, the experimental like the human diabetes insipidus is of different nature from diabetes mellitus.

(*h*) Glycogen injections, lecithin injections, pancreas feeding, and other miscellaneous procedures showed no effect in modifying diabetes [Chapter XVIII.]

(*i*) The liver was concluded to have no specific influence whatever, either in producing or in preventing diabetes.

II. Influences yielding positive results.

(*a*) *Toward Producing Diabetes.* — Two agencies have proved efficient in producing diabetes with a pancreas-remnant of more than the ordinary size.

(1) An irritative nervous lesion. The Bernard puncture produced permanent diabetes gravis in one predisposed dog which was demonstrated to be non-diabetic before the puncture. The characteristic changes in the islands of Langerhans were found at autopsy; it may therefore be possible that nervous influences can produce island-changes. In other predisposed dogs, glycosuria persisting for a number of days has been obtained. The cases are supposed to be analogous to traumatic diabetes in man. It is suggested that most human diabetes is a (probably irritative) disease of the nervous system.

(2) A circulatory disturbance. When the portal vein was rapidly obliterated by the Bernard method, a dog with a relatively large pancreatic remnant developed permanent diabetes gravis. The glycosuria *ex amylo* observed by Bernard in normal animals after this procedure is not explainable on Bernard's hypothesis, but may plausibly be interpreted as a diabetes levis, due to circulatory disturbance in the pancreas. The islands of Langerhans after portal obliteration have been found changed, but not in the same manner or degree as in other diabetic animals.

Conditions have prevented carrying out a satisfactory series of experiments with nervous and circulatory diabetes, and repetition by others is highly desirable, in order to test the conclusions which are here based upon very few animals.

(*b*) *Toward Preventing Diabetes.* One influence in this direction has been suggested and another demonstrated.

(1) The enervation of the pancreas-remnant has seemed to be of service in preventing the more permanent effects of piqûre in predisposed animals. Just as the piqûre produces nervous effects upon the liver, kidneys, and adrenals, so also it presumably acts directly upon the pancreas. The more permanent effects, and the only true diabetic effects, are assumed to be due to action upon the pancreas, and to be prevented by interruption of the pancreatic nerves. Though here also a satisfactory series was not possible, the suggestion has been ventured that operative division of either the splanchnic nerves or the local pancreatic nerves may be advisable in traumatic diabetes. Also, in the large proportion of diabetic cases, not due to gross pancreatic lesions and presumably of nervous origin, it may possibly be advisable either to enervate the pancreas or to graft in a fresh nerve-supply.

(2) Ligation of ducts. The occurrence of diabetes as heretofore described, with pancreas-remnants of definite size when the ducts are left patent, is regularly prevented by ligation of the ducts. Even with still smaller remnants, diabetes may still be prevented. Under favorable conditions, a diabetes already begun may be stopped by ligation of the ducts. In such animals, the curve of tolerance ordinarily rises, until sometimes it attains a considerable height. Finally the curve descends and a late diabetes of the Sandmeyer type ensues. The absence of diabetes with ligated ducts seems to correspond to a better preservation of the islands of Langerhans; the characteristic diabetic degeneration is absent, and the preservation of the islands is regularly demonstrable except when the disorganization of the tissue is such as might obscure islet-cells even if present. The experimental findings have been brought into relation with clinical facts, viz., the absence of diabetes when the ducts have been occluded by calculi without destruction of the islets, the usual absence of diabetes in pancreatic carcinoma, and the termination of an already existing diabetes in certain cases when the ducts have become stopped by carcinoma, the closure of the ducts and the cessation of glycosuria

being synchronous. The otherwise unexplainable effects of oats and certain other foods also receive a reasonable explanation on the basis of these experiments. It has been tentatively suggested that duct-ligation or analogous procedures applied to a part or the whole of the pancreas may possibly possess some curative or palliative value in connection with diabetes. Numerous further experiments, and a conservative weighing of unfavorable possibilities, are recommended before the practical application.

In general, therefore, allowing for a certain number of purely organic cases, the sequence of causation in the average case of human diabetes is presumed to be the following; nervous disorder → impaired function of the islands of Langerhans → deficiency of pancreatic amboceptor → glycosuria and other symptoms. The functional character of the pancreatic disturbance in many or most cases of human diabetes is worthy of all emphasis; for if it is once established, the existing hopelessness regarding this disease is gone forever. Whether the therapeutic measures here suggested succeed or fail, the fact remains that a functional disease must be curable. The rest of the story may safely be left to the numerous and skillful investigators who abound in scientific medicine today.

If the findings reviewed above or most of them are confirmed, the general effect should be to place the subject of diabetes upon a simpler and more rational basis. It is again regretted that conditions have prevented the thoroughness which was aimed at, so that important conclusions require verification by others more fortunately situated. At least, the research has yielded materials and methods — a satisfactory imitation of human diabetes in laboratory animals, predisposed animals as test-objects, the behavior of sugars under different conditions, and various principles in regard to these. Instead of a discouraging tangle, experimental diabetes may be viewed as an orderly series of definite, clean-cut problems. The despair of the clinical disease may be lightened by at least a suggestion of hope. The cure of diabetes is a feasible experimental problem. The entire subject promises valuable results, and it is hoped that numerous workers may undertake the investigation.

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APPENDIX.

METHODS.

Weights and Temperatures.

As a rule, daily records of the weight and temperature of each animal were kept. The weight was taken upon accurate scales, in grams. The temperature was taken by a Fahrenheit clinical thermometer in the rectum, at hours constant for each experiment, either mornings only, or both morning and evening. The morning records were taken generally between 8:30 and 9:30 a.m., and the evening records between 4 and 5 p.m. The exact hour is frequently not stated in the protocol, but the designations a.m. and p.m. in the protocols are to be understood as here stated.

Feeding.

Feeding was at regular hours, in the forenoon unless otherwise specified. In certain experiments, it was found highly convenient to feed at the end of the afternoon. The experimental procedures performed during the forenoon therefore found the animal with empty stomach and less subject to vomiting or digestive disturbances. By the time the evening meal was due, unpleasant effects had generally passed off, and the animal was ready to eat and retain food in the usual manner.

The diet of each animal is accurately recorded in each individual experiment. Cats and dogs were the most numerous species used. For the cats, horsemeat was the routine diet. Meat-diet for dogs is in various ways undesirable. Dog-bread is often eaten poorly, and is especially liable to be refused on the very day of some experiment in consequence of which the animal may be feeling a little out of sorts. Special combinations for metabolic purposes are well known, but have not been used in this series. The necessity for work on as large a scale as the present attempt is a diet which shall be cheap, convenient, healthful, acceptable to the dog, productive of sufficiently firm feces for cleanliness in case of the animals in general and for satisfactory collection in metabolic experiments, and sufficiently constant in composition for the degree of accuracy required in the work for which it is employed. After a few trials, the diet chosen for the dogs was a mixture of bread and meat. Through the courtesy of Dr. Theobald Smith, a large quantity of excellent horse-meat was obtained from the Bussey Institution, free of charge, and other quantities were purchased elsewhere. The meat was kept frozen solid, and freshly autoclaved before feeding. Stale white bread from the bakery was obtainable at minimum cost. When desired, some dogs not in use can be kept on a diet of nothing but bread soaked in soup, on which they do reasonably well. Chunks of bread and meat stewed together can also be used conveniently. But the standard diet for the great majority of the dogs was a mixture of equal parts by weight of cooked horse meat and air-dry bread, passed together through the sausage-grinder. For ordinary feeding, one such grinding and a brief mixing afterward are sufficient, and the mixture is moistened with either soup or water at the time of feeding. For metabolic experiments, the custom was to select uniform-appearing portions of meat prepared under standard conditions, and whole loaves of bread air-

dried in a room, which with the ventilating system in use here means practically standard conditions. For the sake of both accuracy and convenience, a large quantity, if possible enough to last through the whole experiment, was prepared at one time, and after grinding and mixing was passed repeatedly through the sausage-machine till a uniform mass resulted. There were slight differences between different lots, but on the whole the Kjeldahl tests of samples from the different lots and from different portions of the same lot showed a very satisfactory uniformity. The lot thus prepared was kept in frozen condition. For metabolic work, the stated quantity of the mixture was weighed out, and moistened with a stated quantity of hot water, so that the whole mass became of a tepid temperature. This diet has seemed to fulfill all the conditions enumerated above. It is what is referred to, in the frequent record that the dog was fed "bread and meat mixture." Since the preparation is by weight, the bread considerably outbulks the meat. But the dogs eat it with an appetite such as they never show for bread under any other conditions, and they have neither inclination nor ability to pick out the meat from the bread. A dog new to the laboratory rarely requires any forcing in becoming used to the mixture, and after becoming accustomed to it will frequently eat it in preference to meat. A dog on a regular diet of the "coarse" mixture, ground only once, notices no difference when a metabolic experiment is begun with the "accurate" mixture, and therefore eats as usual. A dog fed on a fixed quantity of the "coarse" mixture is in approximate nitrogenous equilibrium all the time, and whenever desired, a metabolic experiment can be begun with brief preparation.

Injections.

The different common sugars and a few related substances were administered by the four convenient routes, by mouth, subcutaneously, intraperitoneally and intravenously.

Oral Administration. — Concerning administration by mouth, there is not much to say. In some cases it is desirable to avoid the use of the stomach tube, and with a little practice, it is possible to give sugar-solutions to guinea-pigs, kittens and even larger animals with a pipette or medicine-dropper, with very little struggling and without losing a drop. For a stomach tube, when one is needed, the rubber catheter passed through a perforated cork which protects it from the animal's teeth, is a laboratory method familiar to all. Dogs easily learn to take the stomach-tube willingly, and require no restraint and no protection for the tube.

Rats, guinea-pigs and rabbits do not vomit. Cats are largely unsuitable for experiments with oral administration of sugar. They persistently vomit solutions stronger than 25 per cent, and also weaker solutions if given in large quantity. Dogs retain sugar better. Very large doses, especially in concentrated solution, naturally lead to vomiting. But if necessary, any quantity of sugar in any concentration desired can be given to a dog. The animal can be placed on a table, under continuous observation, and any attempt to vomit forcibly restrained. If the dose is at all within reasonable limits, and given on an empty stomach, after an hour's watching the danger of vomiting can generally be considered over, and the dog returned to his cage. Diarrhea will soon follow after large doses, but the feces ordinarily give no reduction of copper. The procedure described is practically worthless for cats. A cat closely watched may retain a dose of sugar the whole day, and then when returned to the cage may vomit apparently almost the entire quantity administered.

Intravenous Injections. — The apparatus used for intravenous injections has been essentially the same as that to be described for subcutaneous injection. For the rabbit, a needle into one of the ear-veins is the ordinary method. For the cat, the external jugular vein is first choice, the femoral second choice. For the dog, all methods are available, and the choice is governed by conditions. Even large injections can readily be given through a needle entered into any one of several veins of a dog's ear, which is shaved to bring them into view. Obviously, dogs with large ears are to be preferred

for such work. In other cases, a small glass cannula placed in some small superficial vein, such as the saphenous, is a very satisfactory means of injection. The larger veins are of course available if needed. A general anæsthetic is ordinarily undesirable. By the use of local freezing, or sponging in the wound with a very weak cocain solution, a cannula can be inserted wherever desired, and the dog will show no evidence of pain.

Intraperitoneal Injections. — The instruments are the same as for subcutaneous experiments. The technique requires no remark. Solutions of 10 per cent or even 25 per cent appear to cause no pain. I have never seen an infection or an injury.

Subcutaneous Injections. — Most authors have used syringes for small injections, and a funnel with rubber tubing and needle attachment for large injections. The latter method is feasible, but inconvenient if many injections are to be given; for either the funnel and connections must be cleaned each time, or a whole supply of sterile cumbersome apparatus must be in readiness.

In my experiments, most of the injections of weak solutions have been given by means of a special type of air-syringe used in routine work in this laboratory. It consists of a rubber bulb and stopper and a glass barrel, the nozzle of which is connected with the needle by a short rubber tube. The original form of the syringe is small, delivering about 10 cc.; but I made a supply of larger ones out of glass tubing, large and long enough to deliver 50 cc. or more. The apparatus is compact and convenient, and suited for use by one person without assistance. Occasionally, in later experiments, a small trocar was used in place of a needle. This is the most convenient for single injections, the apparatus consisting only of the long syringe-barrel, rubber connection, and trocar. The trocar allows every drop of the liquid to run in by its own weight; if there is any delay, merely pulling the animal's loose skin away from the end of the trocar creates enough of a vacuum to draw the liquid rapidly out of the syringe.

The above devices serve well for concentrations up to 50 or 60 per cent. Beyond that, sugar-solutions become rather viscous, and the Luer or other ground-glass syringe is the instrument of choice. Considerable pressure is sometimes required to force saturated solutions through the needle.

Gentle animals require no restraint, and for the most part none has been used. Strong solutions may be vigorously resented by cats. It is preferable for all animals to be in a natural position, and for the injection to be given near the middle line of the back. The injection then gravitates downward, and needle-punctures require no sealing, for no liquid escapes. When the trocar is used, it may be advisable to seal the opening with collodion. An animal's body was divided into imaginary areas, — neck, shoulder, mid, rear, flank, — and these were gone over in regular order, so that an injection was never repeated at a given site until all the others had first been covered. When accurate comparisons were necessary, perfectly symmetrical areas on opposite sides of the animal were used for the injections to be compared, though I have never observed any difference between the results in different regions. Very large injections should preferably be scattered over several areas. I have seldom given more than 50 cc. of 10 per cent solution in one place in a cat, or more than 100 cc. in one place in a dog; and higher concentrations are given in proportionally smaller amounts.

The brand of the sugar used is recorded in most experiments. Whenever it is omitted, Kahlbaum's is to be understood. A considerable number of Merck's preparations have been used; very few from other sources. In each experiment, the same brand of sugar was used throughout.

Physiological saline was the solvent in a few of the earlier experiments; but this was abandoned, and throughout practically all the work the sugars were dissolved in distilled water. The amount of sugar desired was weighed out on accurate chemical balances, dissolved in a small quantity of water, and then diluted to an exact volume. For the character of the work, it was entirely unnecessary to check up the solutions by analysis. The analyses that were made showed them satisfactorily accurate.

In round figures, 5 per cent is the isotonic or "physiologic" concentration for the monosaccharides. For the disaccharides, 10 per cent is close enough in round numbers. But for the routine injections, I have used 10 per cent as the ordinary standard for weak solutions of all the sugars, because of the saving in bulk, and because there is not the slightest appearance of any pain or irritation from its use in any animal. All sorts of different concentrations have been used in different individual experiments. But as a standard for routine work with strong solutions, 80 per cent has been the concentration arbitrarily adopted. All such strong solutions are obviously but not excessively painful on injection.

The reason why 80 per cent has been the standard used for comparison between the different sugars in strong solution, is that it is practically the highest limit feasible for lactose. The lactose is dissolved in a larger volume, which is then boiled down to the accurate quantity. This super-saturated solution is injected at a temperature a little above that of the body. The ground-glass syringe for the purpose is taken fresh from the water in which it has been boiled; it is thus both warm and wet, so that the tendency to crystallization upon the glass is diminished. In cases where accuracy demands the giving of the full quantity of sugar, the syringe is cleaned with 2 or 3 cc. of water, solution brought about by boiling, and these washings injected. Promptly after any such injection, the piston of the syringe should be withdrawn from the barrel, to avoid the clogging which results if the solution crystallizes between piston and barrel.

Infection.

Infection never results from any sugar-injection except by fault of the operator. It must be admitted that the higher the concentration and the greater the dose, the more danger there is, especially in a feeble animal such as the guinea-pig. But dextrose of 100 per cent concentration can be injected into the guinea-pig without infection. All strong solutions produce more or less œdema about the site of injection, which passes off in from 12 to 48 hours, according to the concentration and the dose; generally in about 24 hours. Necrosis or sloughing does not occur.

For routine work the weaker solutions are preferable, and one may inject the 10 per cent solution with perfect impunity. In some of the early work, and later in special cases, a small patch of skin perhaps two centimetres in diameter was shaved dry and tincture of iodin dropped on it. The final preparations for the injection were then made while the iodin was drying; after that more iodin was dropped on, and the injection given immediately. Later, for all the ordinary routine injections, nothing whatever was done except to make sure that the syringe and solution were sterile. Even in case of the 80 per cent solutions, the needle was plunged through the skin covered with all its natural hair and unprepared in any way. This was done not only for convenience, but also as a practical test whether the animal's resistance against infection was becoming impaired in consequence of the continued injections.

Animals. — Methods of Obtaining Urine.

The work has included over two hundred dogs, a somewhat smaller number of cats, and still fewer rabbits, guinea-pigs and rats.

No metabolic experiments were performed on rats or guinea-pigs, in which accurate collection of urine is impossible. As is well-known, male rabbits can be catheterized, and the bladder in either sex emptied in approximate fashion by suitable pressure over it. In general, rabbits are not adapted to the sort of experiments required for the present research.

There is no better laboratory animal than the cat. Its health, strength and resistance are of the best. It is quiet, cleanly, contented in confinement, gentle when rightly handled; and yields uniform, consistent results in experiments. Some disadvantage

has attached to it because catheterization is not feasible. The male cat cannot be catheterized; and though catheterization of female cats is said to be possible, it would perhaps be an inconvenient procedure for prolonged experiments. But it is not generally understood that the emptying of a cat's bladder by pressure is even more accurate and satisfactory than the same procedure for the rabbit; and in this way the cat becomes suitable for some kinds of metabolic work. In certain fasting experiments, before I had hit upon this device, it was necessary to start the fast when the cat had voluntarily emptied its bladder, and count the total urine from the beginning of the fast to the autopsy. In similar later experiments it was an easy matter to empty the animal's bladder at regular hours every two or four days. Just as cystitis must be avoided in catheterized dogs, bladder injuries must be avoided in these procedures with cats. If the cats are gentle and accustomed to handling, the process is easy. Young animals, especially females, may let go their urine voluntarily if pressure is made, not suddenly and roughly, but gently and moderately, upon the bladder itself. In animals that are stubborn, especially in old males, an assistant is desirable, who holds the front legs and head and applies an ether mask to the nose, while the operator holds the hind legs with one hand and compresses the bladder with the other. No anæsthetic effect is desired; nothing but the first irritation of the ether to make the cat forget about its bladder. Moderate, continued pressure is the requirement; violence will induce albuminuria or even bladder-hemorrhage. Cats vary in suitability. The process is painless, and a good cat soon learns enough that neither ether nor assistant is needed. The cats which I have used for prolonged experiments have been those which could be placed over a pan, with one hand on the back and the other grasping the bladder, and which then with continued gentle pressure would quietly and voluntarily empty the bladder completely. The cat's bladder is more definitely palpable than the rabbit's. The presence of less than 5 cc. of urine permits recognition and emptying in the case of suitable animals. The pressure is always to be applied by an accurate grasp of the bladder itself, not by a general squeezing of that region.

The dogs used in metabolic work were all females with one exception. The females were prepared for catheterization by the usual procedure of splitting the perineum and sewing skin to vaginal mucous membrane. Slim, narrow-built dogs may be split as far as desired. Broad-built animals of the bull-terrier type, especially those that have been pregnant, are liable to prolapse if the incision is carried too far. The prolapse is easily corrected by perineorrhaphy. It is said that male dogs can be catheterized. Roth indeed asserts that with suitable catheters the process is easy, and he seems if anything to prefer male to female dogs. I have not attempted catheterization of male dogs except after preparatory operation, consisting in a perineal incision, cutting the urethra, and bringing it out to the skin. Catheterization is then easy, especially with a metal or woven catheter. The artificial opening tends gradually to close unless frequently dilated; the normal urethra becomes restored without stricture. Males thus prepared are somewhat less satisfactory than females.

Analyses.

Analyses other than for total nitrogen and for sugar were of necessity omitted, though valuable fields were thus obviously left untouched. There were no respiration experiments.

Nitrogen. — Urine analyses have predominated. When attention to the feces was necessary, it has been demarcated with talcum or charcoal. The nitrogen determinations were all made in duplicate by the customary Kjeldahl method in which copper sulphate is used as a catalyzer.

Sugar. — The Benedict qualitative and quantitative methods have been almost the only ones employed. The experience with both has been very satisfactory. In a very few necessary instances, other confirmatory tests were used.

Blood-sugar. — Blood for sugar-analyses has been collected from a cannula in either the carotid or femoral artery, under brief ether anæsthesia. Control tests have shown values within normal limits, so apparently the anæsthesia was not an important disturbing factor. As the blood-sugar determinations were only an occasional feature, I have not exerted myself to learn any of the numerous new methods, excellent as they are. The first steps have been as described by Röhmann, viz., receiving the blood into saturated sodium sulphate solution, diluting with water, and boiling with addition of acetic acid. After filtration, the residue with the filter-paper was ground in a mortar with additional water till the paper was reduced to fine pulp. The presence of the pulp accelerates filtration. After the fifth filtration, the combined and neutralized filtrates were evaporated to convenient bulk. Sugar was determined by the Benedict titration method.

Urinary Sugar. — Qualitative. For the convenience of those not familiar with the reagent employed, its description may here be presented in the language of the author, Stanley R. Benedict.

	Grams or cubic centimeters.
Copper sulphate (pure crystallized).....	17.3
Sodium or potassium citrate.....	173.0
Sodium carbonate (crystallized)*.....	200.0
Distilled water to make.....	1000.0

"The citrate and carbonate are dissolved together (with the aid of heat) in about 700 cc. of water. The mixture is then poured (through a filter if necessary) into a larger beaker or casserole. The copper sulphate (which should be dissolved separately in about 100 cc. of water) is then poured slowly into the first solution, with constant stirring. The mixture is then cooled and diluted to one liter.

"This reagent is about ten times as sensitive to sugar in urine as is Fehling's or Haines' solution, and unlike these latter solutions is not appreciably reduced by creatinin, uric acid, chloroform or the simple aldehyds. The mixture may be kept indefinitely in uncolored glass or cork-stoppered bottles. Samples prepared over two years ago show no detectable change. Although the reagent is very sensitive for detecting sugar in urine, normal urines give no trace of a reaction when tested with it. An examination of hundreds of samples with the solution served to demonstrate that whenever a positive reaction is obtained, pathological quantities of dextrose are present. Homogentisic acid (from the urine of alkatonurics) or greatly increased amounts of glycuronic acid, both of which substances readily reduce Fehling's solution, will also affect the carbonate-citrate reagent, and when the presence of these substances is suspected, the urine should be tested before and after fermentation with yeast. If the reducing action of the urine is apparent after twenty-four hours' fermentation, the reduction is not due to glucose, but may be due to lactose, or to either of the substances mentioned above. Interference from homogentisic acid is exceedingly rare, and occurs from glycuronic acid only after the ingestion of drugs which lead to increased elimination of this substance.

"In regard to the use of the reagent recommended in this paper, it should be pointed out that until one is familiar with its behavior the following directions should be closely adhered to. The solution is unlike Fehling's reagent in many respects, and should not

* One-half the weight of the anhydrous salt may be used.

be used in the same way as this latter solution. No strongly dehydrating substance (such as caustic alkali) is present in the new reagent, hence its reduction product is apt to be yellow, or even greenish-yellow (consisting of the hydrated suboxid of copper) rather than the red suboxid. For the detection of glucose in urine about 5 cc. of the reagent are placed in a test-tube and *8 to 10 drops* (*not more*), of the urine to be examined are added. The mixture is then heated to vigorous boiling, kept at this temperature for one or two minutes, and allowed to cool spontaneously. In the presence of glucose *the entire body of the solution will be filled with a precipitate*, which may be red, yellow or greenish in tinge. If the quantity of glucose be low (under 0.3 per cent) the precipitate forms only on cooling. If no sugar be present, the solution either remains perfectly clear, or shows a faint turbidity that is blue in color, and consists of precipitated urates. The chief points to be remembered in the use of the reagent are (1) the addition of a small quantity of urine (8 to 10 drops) to 5 cc. of the reagent, this being desirable not because larger amounts of normal urine would cause reduction of the reagent, but because more delicate results are obtained by this procedure, (2) vigorous boiling of the solution after addition of the urine, and then allowing the mixture to cool spontaneously and (3) if sugar be present, the solution (either before or after cooling) *will be filled from top to bottom with a precipitate*, so that the mixture becomes opaque. Since bulk, and not color, of the precipitate is made the basis of a positive reaction, the test may be carried out as readily in artificial light as in daylight, even when examining for very small quantities of sugar. The solution is not dark-colored like Fehling's fluid, so that the precipitate may readily be observed without waiting for it to settle."

Quantitative; Three Solutions. — The work was begun with Benedict's earlier procedure, which requires three separate solutions; and although in the meantime his later method using only one solution has been published, the present work was so nearly completed that the new method was not adopted.

The formula for the three solutions referred to is as follows:

Copper solution.	Grams or cubic centimeters.	Alkaline tartrate solution.	Grams or cubic centimeters.
$CuSO_4$	34.65	Sodium carbonate (anhydrous)	100
Water, to make	500.00	Rochelle salt	173
		Water, to make	500

Ferrothiocyanate solution.	Grams or cubic centimeters.
Potassium ferrocyanide	15.0
Sodium carbonate (anhydrous)	50.0
Potassium thiocyanate	62.5
Water, to make	500.0

Only the copper solution need be made with absolute accuracy. Also in measuring out the solutions for use, only the copper solution requires absolute exactness; the others may be approximate.

For use, equal quantities of the three solutions are mixed; 10 cc. of each is the quantity generally recommended. To the mixture is added from 2.5 to 5 g. anhydrous sodium carbonate, the larger quantity being used in cases when the urine contains only

a small percentage of sugar; that is, cases when the amount of urine to be added will cause the greatest dilution of the solution. The solution bumps unpleasantly in boiling, unless a trifle of talcum powder is added to it. Titration is conducted as in the case of Fehling's solution. As the urine is slowly added, the green-blue color of the solution gradually fades. The end-point is when the last trace of blue color has disappeared, leaving only a chalk-white precipitate in a clear solution.

Calculation is made on the basis that 10 cc. of the copper solution is completely reduced by 0.073 g. of dextrose.

Quantitative; One Solution. — A recommendation of this method is found in the recent paper of Victor C. Myers. The description by Benedict is as follows:

	Grams or cubic centimeters.
Copper sulphate (pure crystallized)	18.0
Sodium carbonate (crystallized)*	200.0
Sodium or potassium citrate	200.0
Potassium sulphocyanate	125.0
Five per cent potassium ferrocyanid solution	5.0
Distilled water to make a total volume of	1000.0

"With the aid of heat dissolve the carbonate, citrate and sulphocyanate in enough water to make about 800 cc. of the mixture, and filter if necessary. Dissolve the copper sulphate separately in about 100 cc. of water and pour the solution slowly into the other liquid, with constant stirring. Add the ferrocyanid solution, cool and dilute to exactly 1 liter. Of the various constituents, the copper salt only need be weighed with exactness. Twenty-five cc. of the reagent are reduced by 50 mg. of glucose.

"Sugar estimations are conducted as follows. The urine, 10 cc. of which should be diluted with water to 100 cc. (unless the sugar content is believed to be low), is poured into a 50 cc. burette up to the zero mark.

"Twenty-five cc. of the reagent are measured with a pipette into a porcelain evaporation dish (25–30 cm. in diameter), 10 to 20 gm. of crystallized sodium carbonate (or one-half the weight of the anhydrous salt) are added, together with a small quantity of powdered pumice-stone or talcum, and the mixture heated to boiling over a free flame until the carbonate has entirely dissolved. The diluted urine is now run in from the burette, rather rapidly until a chalk-white precipitate forms, and the blue color of the mixture begins to lessen perceptibly, after which the solution from the burette must be run in a few drops at a time, until the disappearance of the last trace of blue color, which marks the end-point. The solution must be kept vigorously boiling throughout the entire titration. If the mixture becomes too concentrated during the process, water may be added from time to time to replace the volume lost by evaporation. The calculation of the percentage of sugar in the original sample of urine is very simple. The 25 cc. of copper solution are reduced by exactly 50 mg. of glucose. Therefore the volume run out of the burette to effect the reduction contained 50 mg. of the sugar. When the urine is diluted 1:10, as in the usual titration of diabetic urines, the formula for calculating the per cent of sugar is the following:

$\frac{0.050}{X} \times 1{,}000 =$ per cent in original sample, wherein X is the number of cubic centimetres of the diluted urine required to reduce 25 cc. of the copper solution.

* One-half the weight of the anhydrous salt may be used.

"In the use of this method chloroform must not be present during the titration. If used as a preservative in the urine it may be removed by boiling a sample for a few minutes, and then diluting to its original volume.

"Like the reagent for qualitative employment, the one for quantitative work will keep indefinitely after its preparation. As regards the accuracy of the method, it may be stated that repeated determinations, and comparisons with results by the polariscope and by Allihn's gravimetric process, have shown the method to be probably more exact than any other titration method available for sugar work."

Animal Records.

A few of the most important protocols are here presented in detail. Even for the less important experiments, such as determinations of sugar-tolerance and other incidentals, a complete clinical record was kept for each animal, generally including weighing every day and temperatures either once or twice daily, and such other precautions as necessary to guard against disturbing factors. Expense has prevented the publication of as complete a series of records as desired, and in most cases the brief summaries in the text have had to suffice.

DOG 17.

Female; mongrel, brindle; age 2 years.
Received Nov. 9, weighing 8420g.

Date	Weight g	Temp.	Urine. Quant. cc.	SpG.	Benedict	Alb.	Treatment and Remarks.
Mar. 9	9110	101^6					Removal of pancreatic tissue weighing 18.9g. Remnant communicating with both ducts estimated at 4g.
March 17-28, fasting experiment (see Chapter VI). Final weight 7190g.							
March 29-April 2, diet of sweet cakes, with 100g. or more of glucose or cane-sugar by stomach-tube daily.							
Apr. 3	8730	A.M. 101^8	Specimen 1 P.M. (most of urine lost)		Neg.	Neg.	9.30 A.M., 100cc. 50% glucose by tube. 10 A.M., injected 3cc. 1/1000 adrenalin chloride solution right side, and 100cc. 20% glucose left side. Vomited. Diarrhea. Dog drinks much, but does not eat. Great tenderness at adrenalin site. Has eaten very little.
			Up to 5 P.M. 125	1060 1015	Heavy "	Neg. "	
		P.M. 104	from 5 to 9 P.M. 130	1015	slight	"	
" 4	8200	A.M. 104^6	270	1022	Neg.	Neg.	
May 13	10320	A.M. 102	300	1038	Neg.	"	Dog has had extra feed. Very fat, strong and comfortable. Fed one dozen fresh sheep thyroids. The thyroids are selected so as to weigh always between 45 and 50g. total and are fed at 9.30 A.M. At 5 P.M., the usual diet of 225g. bread-and-meat mixture is fed. Water is constantly in cage. Catheterization 9 A.M. and 5 P.M.
" 14							Fed one dozen thyroids 9 A.M. Evening meal of bread-and-meat omitted by mistake.
" 15	9510	A.M. 101^6 P.M. 101^8	360	1036	Neg.	Neg.	Fed one dozen thyroids.
" 16	9640	A.M. 102	500	1030	Faint	"	One dozen thyroids A.M.
" 17	9570	A.M. 101^8	280	1036	0.26%	"	Thyroids increased; fed two dozen daily; weight is somewhat over 100g.
" 18	9475	A.M. 102^8 P.M. 103^8	480	1028	0.38%	"	Dog seems restless and excitable. Heart is irregular and apparently weak.
" 19	9450	A.M. 102^4 P.M. 102^6	410	1028	0.35%	"	
" 20	9360	A.M. 102^8	390	1032	0.9%	"	10 A.M., subcut. injection of 38g. Kahlbaum dextrose in 60% solution, scattered in 3 areas (about 4g. per kilo). Heart is still irregular. No diarrhea.
			5 P.M. 82	1032	0.4%	"	
" 21	9660	A.M. 101^6 P.M. 102^3	220 5 P.M. 217	1040 1022	1.1% Faint	" "	Appears unusually hungry under thyroid treatment.
" 22	9370	A.M. 102^4 P.M. 102^6	255 5 P.M. 205	1038 1020	0.54% 0.3%	" "	10 A.M., by stomach tube, given 38g. Kahlbaum dextrose in 60% solution (4g. per kilo, the same dose as given subcutaneously on May 20).
" 23	9300	A.M. 102 P.M. 102^2	250 5 P.M. 430	1032 1032	0.33% 5.2%	" "	10 A.M., 200cc. 50% commercial glucose given by stomach tube. Drinks much and often. Slight diarrhea toward evening.
" 24	9200	A.M. 102^4 P.M. 102^6	250 5 P.M. 290	1030 1030	Neg. 4.56%	" "	10 A.M., fed 100g. Kahlbaum dextrose dry, and watched to prevent vomiting. Drank 570cc. water between dextrose and 5 P.M. Measured water in cage over night.

DOG 17 (Continued).

Date	Weight g.	Temp.	Urine				Treatment and Remarks.
			Quant. cc.	SpG.	Benedict	Alb.	
May 25	9200	A.M. 102^2	490	1016	Neg.	Neg.	Drank no water during night. Thyroid feeding discontinued.
" 26	9200	A.M. 102 P.M. 102^2	310	1030	"	"	
" 27	9220	A.M. 101^8	Specimen	1020	"	"	
" 28	9170				"	"	Given exercise.
" 29	9160	A.M. 101^8	8.30 P.M. 46	1042	"	"	Catheterized at 9.30 A.M. Dog is to fast 24 hours. 600cc. water left in cage. Catheterized 8.30 P.M. Drank 75cc. up to this time. 600cc. left in cage over night.
" 30	8910	A.M. 101^4	35	1052	"	"	Catheterized 9.30 A.M. Has drunk 40cc. water during night.
June 5	9260	A.M. 101^8	1 P.M. 30	1032	2.1%	"	Catheterized at 9.30 A.M. Is to fast 24 hours. Injection of 4.5cc. 1/1000 solution adrenalin chloride, left side. Catheterized at 1 and 4.30 P.M. Drank 275cc. water up to 8.30 P.M. Catheterized midnight.
			4.30 P.M. 45	1056	3.8%	"	
		P.M. 103	8.30 P.M. 180	1025	0.6%	"	
			Mid-night 42	1028	Faint	"	
" 6	9195	A.M. 102^8	9.30 A.M. 80	1040	Neg.	"	Drank 80cc. water during night.
" 9	9580						
" 16	9960	A.M. 101^8	9.30 A.M. Specimen		Neg.	"	Is to fast 24 hours. At 9.45 A.M. injected subcutaneously 5cc. 1/1000 adrenalin chloride solution left flank.
			11.30 A.M. 4		Slight	"	11.30 A.M., dog panting, restless. Between 11.30 and 11.45 injected 100cc. 80% Kahlbaum dextrose along right side (a little over 8g. per kilo).
			1 P.M. 70	1040	9.1%	"	Refused water at 12 noon; restless. 12.20 P.M. drank 285cc.; at 2 P.M. drank 365cc. and vomited it immediately.
			3 P.M. 60	1030	12.1%	"	Dog is very restless. 2.15 P.M. drank 120cc. 2.50 P.M. drank 220cc. At 4 P.M. 400cc. clear vomitus found in pan. At 5 P.M. drank 130cc. At 5.45 drank 115cc. Since 5 P.M., excitement has given way to malaise, though periods of excitement still occur. At 8 P.M. drank 215cc. At 8.30 P.M. refused water. Sick and restless. 11 P.M., sick. Refuses water.
		P.M. 100^6	5 P.M. 18	1044	10.4%	"	
			8.30 P.M. 10	1052	2%	slight	
			11 P.M. 9	1050	1%	very "	
" 17	10075	A.M. 102^2	60	1040	Faint	Neg.	Catheterized at 9.30 A.M. Refused water. Would eat, but not fed. Refused water 1 P.M. Acts fairly well. Catheterized 5 P.M. Large bullae still present, as if adrenalin had delayed absorption of sugar solution. Area of necrosis opened at site of adrenalin.
		P.M. 103^6	5 P.M. 80	1047	Neg.	"	
" 18	9350	A.M. 102^4	360	1025	"	"	Catheterized at 9.30 A.M.

DOG 21.

Female; mongrel, yellow, age 2 years.

Date	Weight g.	Temp.	Water cc.	Urine. Quant. cc.	Appear.	React.	Sp.G.	Benedict	Nitrogen g.	Treatment and Remarks.
Dec. 6	6145									Received.
" 18	5600			160	amber	acid	1044	Neg.		Starvation begun. Catheterized at 9:30 a.m. Water to be measured.
" 19	5420	9:30 A.M. 101.6	35	52	amber	acid	1042	Neg.	1.47	Catheterized daily at 9:30 a.m. and 4:30 p.m.
		4:30 P.M.								
		101.4	15	10	amber	acid		"		
" 20	5255	9:30 A.M. 101.2	50	20	amber	acid	1054	Neg.	1.43	Subcutaneous injection of 19.6 cc. 80% Merck dextrose (3g. per kilo.)
				(Total for 24 hours 30 cc.)						
		2 P.M.	15							
				4:30 P.M.						
		101.6	80	13	amber	acid		Slight		
" 21	5160	9:30 A.M. 101.4	25	30	amber	acid	1052	Faint		
		(Total for 24 hours 43 cc.----0.54							2.03	
		P.M.		4:30 P.M.						
		101.2		6	dark			Neg.		
" 22	5070	9:30 A.M. 100.4	35	14	amber	acid	1074	"	1.16	
				(Total for 24 hours 20 cc.)						
				4:30 P.M.						
				10	deep amber	acid		Neg.		
" 23	5000	9:30 A.M. 99.8	85	8	amber	acid		"	1.39	Evening catheterization omitted.
				(Total for 24 hours 18 cc.)						
" 24	4870	9:30 A.M. 102.	35	20	amber	acid	1068	Neg.	1.2	Beginning to-day, dog receives 100 cc. water by stomach tube at 9:30 a.m. and 4:30 p.m. (200 cc. daily) No other water given. Evening catheterization omitted.
			100							
" 25	4820	9:30 A.M. 99.8	100	84	amber	acid	1030	Neg.	1.4	Evening catheterization omitted.
			100							
" 26	4730		100	110	amber	"	1022	"	1.85	Evening catheterization omitted.
			100							
" 27	4590	9:30 A.M. 101.	100	122	amber	"	1020	"	1.79	At 10 a.m., injection of 17.8 cc. 80% Merck dextrose into ear vein (3g. per kilo.) Duration of injection 3 minutes.
				4:30 P.M.						
			100	38		"	1026	2.6%		
		(Urine slightly bloody. Albumin boiled out.)								
" 28	4500	9:30 A.M. 100.4	100	90			1020	Neg.		
		(Still a little bloody. Albumin boiled out.)								
				(Total for 24 hours 128 cc.)					1.83	
		4:30 P.M. 100.	100							Evening catheterization omitted.
" 29	4400	9:30 A.M. 101	100	148	amber	acid	1014	Neg.	2.1	
				4:30 P.M.						
			100	58	turbid	acid	1014	"		
" 30	4350	9:30 A.M. 100.6	100	76	amber	acid	1024	"		Subcutaneous injection of 38.06 cc. 80% Merck dextrose (7g. per kilo)
				(Total for 24 hours 134 cc.)					2.52	
				4:30 P.M.						
		102.2	100	40	amber	acid	1015	Slight		
" 31	4250	9:30 A.M. 101.8	100	20	dark	acid	1052	Faint 0.25%	1.61	Dog is decidedly weak. Still showed thirst after receiving morning water; but at evening was not thirsty, so the usual 100 cc. was given by tube. Diarrhea.
		(Total for 24 hours 60cc.)								
				4:30 P.M.						
		99.6	100	30	(Contaminated with diarrheal feces. Discarded.)					
Jan. 1	4150	9:30 A.M. 101.1	100	210	pale amber	acid	1016	Neg.		Diarrhea. 14.5g. dextrose fed in solid form, animal eating it eagerly. (3.5g. per kilo.) Evening not thirsty; 100cc. water by tube.
		(Total for 24 hours 240cc. Discarded)								
				4:30 P.M.						
		99.7	100	47	amber	acid	1020	Neg.		

Date	Weight G.	Temp.	Urine						Feces		Treatment and Remarks.
			Quant. cc.	Appear.	React.	Sp.G.	Benedict	Nitro. g.	Dry	Nitro. g.	
Jan. 2		9.30 A.M. 100.	10f (Contaminated with diarrheal feces).				Neg.				Full feeding begun.
Feb. 3	6120						Dog is now to be catheterized at 9.30 A.M. daily, and receive 100cc. water by tube. At 4.30 P.M. to receive 100cc. water by tube, and to be fed 250g. bread-and-meat mixture moistened with 200cc. water.				
" 9	6200	9.30 A.M. 101.4 4.30 P.M. 101.5	300	straw	acid	1002	Neg.	4.7	18	0.98	Feces dark, hard.
" 10	6320	9.30 A.M. 101.8 4.30 P.M. 101.4	275	straw	alk.	1022	"	3.1	9	0.52	Feces hard, dark.
" 11	6255	9.30 A.M. 101.6	350	straw	alk.	1020	"	4.53	19	1.08	Feces dark, pasty.
" 12	6220		290	"	"	1024	"	4.73	12	0.69	Feces dark, pasty.
" 13	6270	9.30 A.M. 102.2	265	"	"	1028	"	4.93	9	0.52	Feces dark, pasty
			Catheterized at 12 M. 75 straw " 1010 Catheterized at 4.30 P.M. 25 amber " 1020 Total P.M. 100cc.					0.78			
" 14	6175	9.30 A.M. 101.7	150	straw	alk.	1032	"	3.78	8.7	0.28	Feces hard. Injection of 24.7cc. 50% Kahlbaum dextrose (2g. per kilo) into ear-vein. Duration of injection 5 minutes.
			Catheterized at 12 M. 46 pale straw		alk.	1026	2.9%				
		4.30 P.M. 101.8	30	pale amber		1024	Faint				
			Total P.M. 76cc.					1.28			
" 15	6250	9.30 A.M. 102.2 4.30 P.M. 102.	170	amber	alk.	1030	Neg.	3.64	11	0.62	Feces firm.
			60	straw		1020	"				
" 16	6290	9.30 A.M. 102.	140	straw	acid	1040	Faint				
			Total for 24 hours 200cc.					4.6			
		P.M. 4.30 P.M. 101.4	82	amber	acid	1020	"		16	1.03	Feces diarrheal.
" 17	6260	9.30 A.M. 101.2	130	amber	acid	1040	Slight		22	0.85	Feces diarrheal. Immediately after catheterization at 9.30 A.M., was given by stomach tube the usual 100cc. of water, containing in solution 62.5g. Kahlbaum dextrose (10g. per kilo. Total volume of solution about 130cc.) Dog watched continuously, to prevent vomiting, or diarrheal contamination of urine. At 10.15 A.M. a copious yellow diarrheal defecation. At 11 A.M. spontaneous urination. At 5.30 P.M. a diarrheal defecation. Eats with usual appetite.
			Total for 24 hours 212cc.					5.14			
			11 A.M. (Spontaneous) 8	pale amber	acid	1036	1%				
		4.30 P.M. (Catheterized) 102.4	35	pale amber	acid	1035	Neg.				
" 18	6390	9.30 A.M. 102.6	115	amber	acid	1048	Faint		14	0.9	Feces diarrheal. Water per tube 100cc. at 9.30 A.M. and 4.30 P.M. continues. Morning and evening catheterization.
			Total for 24 hours 158cc.					4.51			
		4.30 P.M. 9 P.M. 101.2	80	straw	acid	1012	Neg.				
" 19	6260	9.30 A.M. 102.	170	pale amber	acid	1030	Faint		8	0.526	Collection of feces discontinued.
			Total for 24 hours 250cc.					5.32			
		4.30 P.M. P.M. 102.4	135	pale amber	acid	1013	Neg.				

DOG 21 (Continued).

Date	Weight g.	Temp.	Urine						Treatment and Remarks.
			Quant. cc.	Appear.	React.	Sp.G.	Benedict	Nitro. g.	
Feb. 20	6320	9.30 A.M. 102.	155	amber	alk.	1040	Faint		
			Total for 24 hours 290cc.					5.03	
		4.30 P.M. 101.8	85	amber	acid	1026	Neg.		
" 21	6340	9.30 A.M. 101.8	150	amber	acid	1038	Faint		
			Total for 24 hours 235cc.					4.8	
		4.30 P.M. 101.6							
" 22	6310	9.30 A.M. 101.6	230	amber	alk.	1028	Neg.	4.13	
Mar. 12	6225								Dog has been on diet of 250g. bread-and-meat mixture. Today the diet was reduced to 225g. Otherwise the daily program is like that instituted February 3.
" 13	6295	9.30 A.M. 101. 4.30 P.M. 101.6	225	amber turbid		1022	Neg.		
" 14	6295	9.30 A.M. 101.6 4.30 P.M. 101.6	270	pale amber	acid	1026	Neg.		
" 15	6260	9.30 A.M. 101.6 4.30 P.M. 101.6	460	amber	alk.	1020	Neg.	4.96	
" 16	6200	9.30 A.M. 101.4	225	amber	alk.	1030	Neg.	4.91	At 10 A.M. dog was tied out supine on table in cool room. Neck shaved. Dog is of nervous disposition, and worried greatly. Toward 11 A.M. external jugular vein was cannulated without anaesthetic, dog struggling and crying.
			9.30-11 A.M. (before ether and injection).						
			15	pale straw	acid	1014	Neg.		
			11-11.30 (period of injection)						
			100	very pale	faintly acid (faintly tinged with hemoglobin)	1025	3.6%		
			11.30-12						
			46	water-pale	"	1028	4.6%		
			12-12.45 P.M.						
			13	very pale	"	1030	5.2%		
			12.45-1.15 P.M.						
			10	very pale	acid	1040	5.2%		
		P.M. 103	8 P.M.						
			70	straw	acid	1025	1.2%		
			Total urine to 8 P.M. 254cc. Faint albumin, not removed.					2.33	At 11.30 A.M. dog was catheterized, and quickly and deeply etherized. Injection into vein of 50cc. 50% Kahlbaum dextrose solution (4g. per kilo), given slowly and intermittently, so that duration of injection was from 11 to 11.30 A.M. Deep anaesthesia continued; body wet and cold. Between 12.30 and 12.45, left femoral artery was cannulated, and blood from it received into sodium sulphate solution. Exact weight of blood sample 58.9g.; blood-sugar 0.396%. Dog catheterized at 11.30, 12, 12.45 and 1.15. At 1.15 anaesthesia was stopped and dog returned to cage. Shivers and acts miserable all day. At 4.30 P.M. the usual water by tube, and evening feed. Dog eats poorly, but after a few hours has finished the full meal.
" 17	5920	9.30 A.M. 103.2	150	amber	alk.	1032	0.3%	1.3	
			(Total for 24 hours 405cc.---------3.63)						
		4.30 P.M. 102.6							
" 18	6050	9.30 A.M. 102.	230	dark amber	alk.	1036	Neg.	5.6	
" 19	6175	9.30 A.M. 101.	240	amber		1030	Neg.	5.23	

DOG 63.

Male; white with brown spots. Thin, choreic and slightly altered mentally from distemper. Has recently and imperfectly recovered from the active disease.

Date	Weight G.	Temp.	Urine					Treatment and Remarks.
			Quant. cc.	Appear.	React.	SpG.	Benedict	
June 5	5990							Perineal hypospadias established by operation under ether (for catheterization).
" 9	7080							
" 12	6980							
" 13								Partial removal of pancreas. Part removed weighed 16.75g. Aside from a few tiny shreds, there is an irregular remnant communicating with both ducts, and estimated to weigh 4.7g. Vessels intact. Omental covering.
" 14		A.M. 102	(No urine passed)					
" 15		12 M. 104^8	200	amber	alk.	1020	Neg.	
" 16		A.M. 103^6	220	"	"	1020	"	
" 17	5970	A.M. 103^7		Specimen			"	Severe distemper in nose. Refuses milk, but takes a little meat. Distempered diarrhea.
" 18		A.M. 103^2		Specimen			"	Signs of active distemper have disappeared.
" 27	6550	A.M. 103		Specimen			"	Signs of active distemper are absent, except temperature. Catheterized at 9 A.M. and starvation begun.
		P.M. 103^4						Catheterized at 4.30 P.M., and urine discarded.
" 28	6140	A.M. 102^8	140	amber	alk.*	1030	Neg.	Daily routine is as follows: Catheterized at 9 A.M., and 200cc. water given by stomach tube.
			4.30 P.M.					
		P.M. 102^6	90	"	"	1012	"	Catheterized at 4.30 P.M., and 200cc. water given by stomach-tube.
" 29	6010	A.M. 101^6	250	straw	"	1010	"	
		P.M. 101	4.30 P.M.					
			100	"	"	1016	"	
" 30	5880	A.M. 101	200	"	"	1012	"	Between 9 and 9.30 A.M. injected 500cc. 0.85% NaCl subcut. along left side.
			1 P.M.					Catheterized at 1 P.M.
			135	"	"	1010	"	
		P.M. 101^4	4.30 P.M.					
			45	amber	"	1018	"	
			Total P.M. urine 180cc.					
July 1	5850	A.M. 100^8	400	straw	alk.	1010	"	
		P.M. 101^5	4.30 P.M.					
			228	"	"	1005	"	
" 2	5660	A.M. 100^8	167	amber	"	1010	"	
		P.M. 101^1	4.30 P.M.					
			100	straw	"	1008	"	
" 3	5580	A.M. 100^8	175	"	"	1010	"	Between 9 and 9.30 A.M., injected 500cc. 10% Merck dextrose subcut. along right side.
			1 P.M.					Catheterized at 1 P.M.
			130	amber	"	1020	3.6%	
		P.M. 100^8	4.30 P.M.					
			12	"	"		7.3%	
			Total P.M. Urine 142cc.					
" 4	5645	A.M. 101^2	325	straw	alk.	1006	Neg.	
		P.M. 102^1	4.30 P.M.					
			255	"	"	1005	"	

*This dog's urine was regularly alkaline, doubtless from cystitis; but albumin never amounted to more than faintest opalescence when boiled with acetic.

Date	Weight g.	Temp.	Urine: Quant. cc.	Appear.	React.	Sp.G.	Benedict	Treatment and Remarks.
July 5	5370	A.M. 100.6	155	straw	alk.	1008	Neg.	Catheterized at 9 A.M. Feeding begun (bread- and meat mixture).
" 6	5640						"	
" 8	5450						"	Diarrhea. Weak.
" 10	5855						"	
" 12	6150						"	
" 14	6015						"	
" 17	6350							Urine has remained free from sugar.

The animal is in medium or rather poor condition. Was fed heavily yesterday; last full meal (meat) at 9 P.M. yesterday. A little meat was also fed early this morning. Etherized at 2 P.M., sugar-puncture done at 2.15 P.M. Recovers well from anaesthetic, with partial paralysis of left side. Vomits meat. Bladder emptied at operation, but at 3.30 P.M., urine found in pan.

		3.30 P.M. 95	light straw	acid	1022	3.5%	
		4.15 P.M. 40	"	"	1030	5.6%	
		6 P.M. 72	" turbid.	"	1032	6.1%	Marked iodoform test in distillate. No diacetic.
		7.30 P.M. 33	straw, slightly turbid.	"	1036	5.6%	Marked iodoform test in distillate. No diacetic. Slight diabetic odor.
		10 P.M. 72	straw, clear	"	1036	2.8%	Decided sweet diabetic odor. Heavy iodoform test in distillate. No diacetic. All urine free from albumin.
July 18		9 A.M. 75	amber	alk.	1034	2%	Paralysis slightly less than yesterday. Diabetic odor. Heavy acetone. No diacetic.
							At 9 A.M., 200cc. 10% dextrose given by stomach-tube. No vomiting.
		10.30 A.M. 57	"	"	1030	6%	Strong diabetic odor. Diacetic neg. as usual. Acetone pos. in urine without distilling.
		11.30 A.M. 97	light straw	acid	1033	12.1%	200cc. 10% dextrose given by tube. Marked iodoform test in distillate. Diabetic odor negative or very faint.
		1 P.M. 120	straw	alk.	1032	12.1%	Diabetic odor negative. Negative iodoform test in distillate.
		3 P.M. 123	pale straw	acid	1033	9.1%	No diabetic odor. Iodoform test faint or neg.

Fed forcibly 18g. pancreas freshly removed from Dog 59, and by tube, 175cc. milk. No attempt to vomit. Pricks up ears, wags tail, but cannot stand on account of left hemiplegia and turning of head to left.

		6 P.M. 55	straw	acid	1040	8.1%	Diabetic odor mod. Well-marked iodoform test.

At 8 P.M., dog is obviously hungry, but eats with difficulty. 75g. beef-pancreas placed in mouth was swallowed willingly; then 250cc. milk was given by tube.

		10.30 P.M. 174	straw	acid	1038	8.4%	Diabetic odor moderate. Well-marked iodoform test. Can sit up a trifle. Milk 250cc. by tube.
July 19	5355	A.M. 101.8	310	amber	alk.	1040	7.3%	Diabetic odor. Iodoform test positive.

Shows little tendency to eat unaided, but swallows willingly. Lies on side unless propped up. At 10 A.M., fed forcibly 150g. beef-pancreas and 150g. dry bread soaked in soup. Noon, drinks a little water voluntarily. Vomited. Vomited again at noon; most of bread given has now been lost, but all of pancreas is retained.

		1 P.M. 230	amber	alk.	1040	12.1%	Diabetic odor. Faint iodoform test.
		4.30 P.M. 190	"	"	1040	9.1%	Diabetic odor. Iodoform test well-marked.

At 6 P.M. was howling for water, and drank a very large quantity.
At 8 P.M. 250cc. milk by tube. Midnight, 300cc. milk by tube.

DOG 63 (Continued).

Date	Weight g.	Temp.	Urine					Treatment and Remarks.
			Quant. cc.	Appear.	React.	SpG.	Benedict	
July 20	5690	A.M. 101	625	amber	alk.	1040	9.1%	All urines henceforth show well-marked diabetic odor and acetone test, but always negative diacetic tests.
			1 P.M.					Milk fed by tube. Sits up with difficulty, but will not eat or drink. Fed forcibly 250g. beef. Distemper showing up in nose and eyes. Feces to date have been very soft but well digested.
		P.M. 101.6	150	"	"	1032	12.1%	
			4.30 P.M.					4 P.M., fed 300g.beef forcibly.
			80	"	"	1030	10.7%	6 P.M. still refuses water. 250cc. given by tube, and part vomited.
" 21	5610	A.M. 103.2	420	"	"	1044	9.1%	Feces becoming harder. Will not eat or drink. 250cc. water given by tube.
			1 P.M.					At 10.30 A.M., fed forcibly 300g. beef.
			200	"	"	1044	7.3%	Feces almost back to normal appearance.
		P.M. 102.6	4.30 P.M.					At 9 P.M., drank 650cc. water, with some difficulty but without stopping. Fed forcibly 300g. beef.
			103	light amber	"	1050	7.3%	
" 22	5770	A.M. 101.8	550	"	"	1044	6%	Refuses to drink. 250cc. water given by tube. Refuses to eat; and at 11 A.M., 300g. beef fed forcibly.
			1 P.M.					Noon, refused water. One defecation, soft, black, well-digested.
		P.M. 103.3	112	yellow	"	1038		
			5 P.M.					Will not drink, so 500cc. water given by tube.
			110	"	"	1043		
			Total P.M. urine 222cc.				6.6%	
" 23	5710	A.M. 101.8	515	yellow	alk.	1033	4.1%	Drank 350cc. water voluntarily.
		P.M. 102.8	5 P.M.					Drank 360cc. " "
			220	amber	"	1040	5.3%	Fed like yesterday.

DOG 63 (Continued)

Date	Weight g.	Temp.	Water cc.	Urine					Treatment and Remarks.
				Quant. cc.	Appear.	React.	Sp.G.	Benedict	
July 24	5615	A.M. 102^6	715	510	Yellow	alk.	1040	5.2%	10.30 A.M., 500g. beef fed forcibly. Noon, a soft gray defecation, poorly digested, with a little blood.
		P.M. 102^8	190	5 P.M. 375	"	"	1022	2.8%	Low sugar due to poor digestion.
" 25	5310	A.M. 102^5	430	390	"		1037	4 %	Diarrhea of poorly digested feces, and vomiting of partially digested meat. Disturbance is due to typical distemper; the feces contain blood, the eyes are purulent, the nose is plugged with thick mucous. Starvation begun.
		P.M. 101^1	105	165	light amber	"	1016	1.1%	
" 26	5440	A.M. 101^2	280	170	amber	"	1028	1.1%	
		P.M. 101^1	155	5.30 P.M. 120 (contaminated with feces)				1.2%	
" 27	5320	A.M. 101	150	150	amber	alk.	1022	0.25%	
		P.M. 101^7	195	120 (contaminated with feces)				0.7%	Still has black diarrhea on starvation, another evidence of distemper.
" 28	5070	A.M. 101^3	125	140	amber	alk.	1014	Faint	
		P.M. 101	105	5 P.M. 135	"	"	1012	"	Diarrhea continues.
" 29	4910	A.M. 101^3	20	140 (contaminated with feces)				Neg.	Paralysis improving slowly. Starvation ended. Fed 300g. lean and fat beef. All eaten greedily but with difficulty, chiefly owing to paresis of one cheek.
		P.M. 103	160	5 P.M. 170	amber	alk.	1017	1.4%	Has vomited 225g. of feed, undigested. Evening, gray, fatty diarrhea.
" 30	4600	A.M. 101^2	140	175	deep amber	acid	1030	2%	Will eat nothing; therefore 75g. beef and 75g. pancreas fed forcibly.
		P.M. 101^9	150	5 P.M. 105	"	"	1037	4.6%	No vomiting or diarrhea during day.
" 31	4850	A.M. 101	210	170	"	"	1030	2.4%	100g. pancreas and 200g. beef fed forcibly. No diarrhea. Dog is weak. Noon, two small soft, dark defecations.
		P.M. 102^2	350	4.30 P.M. 125	amber, turbid	"	1030	3.6%	Evening, fed forcibly 50g. pancreas and 150g. beef.
Aug. 1	4970	A.M. 101^8	180	475	amber	"	1030	4.5%	Today began regular diet of 400g. beef, well cooked after weighing raw, and 100g. horse-pancreas, raw and fresh, all fed forcibly.
		P.M. 102	260	4.30 P.M. 195 (also a small quantity,	"	"	1040	6% perhaps 50cc. lost.)	
" 2	4700	A.M. 100^6	250	400	amber	acid	1042	4.5%	Daily routine as follows: Catheterized at 9 A.M., and 250cc. water given by tube. Catheterized at 5 P.M., and 250cc. water by tube.
		P.M. 101^5	250	5 P.M. 240	deep amber	"	1042	4.6%	Afternoon, one soft defecation, rather poorly digested. Vomited a small quantity of feed toward evening.
" 3	4780	A.M. 101^2	250	250	amber	"	1030	2.6%	At 9-9.30 A.M., injected 40cc. 60% Elmer and Amend dextrose along right side. Vomited all his feed. Very weak. Given by tube 250cc. water, quickly vomited.
		P.M. 102	250	5 P.M. 210	straw	"	1032	5.2%	
" 4	4525	A.M. 99^4	20	30	amber	"	1014	1.7%	No diabetic odor. Iodoform test faint. Diacetic Neg. Only 20cc. water given by tube on account of vomiting. Dog very weak, apparently moribund. Afternoon, death.

Autopsy: Heart and lungs normal. Liver very fatty. Peritoneum fairly free. Adhesions are light and easily broken down. Viscera all appear normal. The pancreas remnant is smoothly covered by omentum. On section, a pea-sized cyst is found near upper pole, as if some small duct had been occluded. Otherwise the tissue is of normal appearance and consistency, and the weight, after emptying the cyst, is 5.55g. The lesser duct was not found, but the complete patency of the main duct was easy to demonstrate. In the lower part of the floor of the fourth ventriole is a considerable transverse wound, extending somewhat more to the right than to the left of the median line.

For microscopic findings see Chapter XXI.

DOG 73.

Female; black and white, long-legged, nervous.

Date	Weight g.	Temp.	Urine. Quant. cc.	Urine. SpG.	Treatment and Remarks.
Aug. 17	12560				Received. Perineum split.
" 28	12900	A.M. 102			Under ether, a loop of No. 3 picture wire was passed around portal vein, ends protruding outside belly.
" 29		A.M. 101^{2}			
" 30		A.M. 102^{3}			Has been vomiting.
" 31		A.M. 103^{3}			Hungry.
Sept. 1		A.M. 103^{1}	960	1010	Dog is lively and very hungry. Has been passing large quantities of urine daily, with some diarrhea. No defecation the past 24 hours, and the urine was accurately collected. Not fed. Catheterized.
" 2		A.M. 102^{7}	390	1012	Catheterized.
" 3		A.M. 102^{7}	450 (contaminated with feces)		Is very lively, strong and hungry. Still a slight diarhea; allowed to take a small meal of dog-bread; eats greedily.
" 4	11370	A.M. 102^{2}	(large quantity mixed with feces)		Diarrhea continues. Dog-bread diet.
" 5	11300	102^{1}	1200	1012	
" 6	11700	A.M. 101^{9}	1100 (containing diarrheal feces)		Drinks copiously, eats heartily. Fed 500g. meat and some bread with soup.
" 7	12000	A.M. 102^{2}	1200	1020	Eats bread and soup heartily every day, and acts well. Feces a little better.
" 8	12400	A.M. 102^{4}	1000 (with diarrheal feces)		Excellent health.
" 9	12150	A.M. 101^{5}	1850 100	1010 1005	Eats hugely, drinks more hugely.
" 10		A.M. 102	1500	1010	Has eaten poorly to-day, but is lively. Feces apparently poorly digested; soft, diarrheal. On roof for exercise.
" 11	12320	A.M. 102^{7}	1400 (passed since return from roof yesterday noon)	1008	Appetite good.
" 12	12100	A.M. 102^{6}	2675	1002	To-day's urine was almost a complete 24-hour specimen, but some was lost on roof. Lively. Feed increased. Given a bone.
" 13	12725	A.M. 101^{5}	2425 (since yesterday noon)	1004	Urine always very pale, free from sugar and albumin.
" 14	12575	A.M. 102^{1}	1725 (since yesterday noon)	1010	Ate very little, but feces are better.
" 15	12600	A.M. 102^{3}	1100 (about 23-hour specimen)	1010	
" 16	12200	A.M. 103^{3}	(urine spoiled by spilled water)		
" 17		A.M. 105^{1}	1300	1010	
" 18	12200	A.M. 104^{4}	925	1010	Lively. Good appetite. Feces soft.
" 19	12600	A.M. 101^{9}	650 (16-hour specimen)	1011	
" 20			825 (since yesterday noon)	1010	
" 21	13000	A.M. 102^{1}	1675	1012	
" 22	12940	A.M. 101^{4}	2125 (since yesterday noon)	1010	Diarrhea.
" 23	13320	A.M. 101	1735 (since yesterday noon)	1006	
" 24	13635	A.M. 100^{7}	1775 (since yesterday noon)	1004	
" 25	13250	A.M. 101^{2}	2000 (since yesterday noon)	1010	
" 26	13330	A.M. 101^{2}	2425 (since yesterday noon)	1004	
" 27	13480	A.M. 100^{6}	1950 (24-hour specimen)	1010	Has only slightly diarrheal yellowish feces. Eats about three times as much as normal dog, and drinks enormously.
" 28	13025	A.M. 104^{5}	1555 (21-hour specimen)	1006	A pull brought the wire out, apparently without damage. Dog eats very well and lively, but has eaten less than usual to-day.

Date	Weight g.	Temp.	Urine. Quant. cc.	Urine. SpG.	Treatment and Remarks.
Sept. 29	13150	A.M. 103	2225 (24-hour specimen)	1010	Has eaten hugely. Feces soft, but good, and not too bulky.
" 30	13200	A.M. 101^{8}	2000 (24-hour specimen)	1010	Feces soft, good.
Oct. 1			2300	1008	
" 2	13600	A.M. 100^{1}	1350	1010	Still eating bread and soup in enormous quantity.
" 3	13400	A.M. 101^{5}	2200	1008	Sinus practically healed. On roof part of day. Given 350g. meat, and a bone. Later, given one kilo. more of meat. Ate all the meat except 275 g.
" 4	13050	A.M. 101^{6}	1600	1018	Has vomited the whole of yesterday's meat, and seems a trifle depressed. Dark diarrhea.
" 5	13060	A.M. 102^{2}	1725	1013	Has eaten little meat, but drunk about two litres water. Very lively. Fed 500g. meat. On roof for exercise.
" 6	12725	A.M. 102^{1}	1200 (18-hour specimen)	1010	Left 75g. out of yesterday's 500g. meat. Drank several litres water. On roof for exercise. Fed 400g. meat.
" 7	13300	A.M. 101^{3}	2450 (16-hour specimen)	1007	All feed eaten. Fed 500g. meat, eaten promptly.
" 8		A.M. 101^{5}	2000	1013	Fed 1 kilo. meat, all eaten within a short time. On roof for exercise.
" 9	13325	A.M. 101^{1}	1935 (20-hour specimen)	1012	Starvation begun.
" 10	13140	A.M. 101^{2}	285 (18-hour specimen)	1007	Drinks less than when fed.
" 11	13000	A.M. 101^{8}	715 (24-hour specimen)	1018	Removal of splenic end of pancreas, weighing 14.4g. Pancreas itself came easily, but operation was long and difficult on account of adhesions and hemorrhage, the latter both from the adhesions and from the congested normal tissues.
" 12			(Up to 12:30 p.m. operation-time yesterday) 350	1012	
			(Since operation yesterday) 325 (with considerable feces and vomitus)		Found in extreme collapse. Died about 9 a.m.

AUTOPSY.

This shows no cause for death, which evidently was due to collapse of a dog below normal strength. Heart and lungs negative. No exudate or any sign of infection in peritoneum. Peritoneal and general body fat abundant. Liver appears normal in size, perhaps a trifle mottled, and slightly fibrous under the knife. Portal vein represented only by scar tissue at site of ligature. Remnant of pancreas weighs 13.9g. and appears entirely normal. Adrenals rather small, but look normal. Kidneys small; together weigh 90g.

For microscopic findings see Chapter XXI.

Male; mongrel, brindle; age 3 years. Medium flesh.

Date	Weight	Temp.	Urine			Treatment and Remarks.
			Quant. cc.	Spg.	Benedict	
Sept. 29						Received. Starvation
Oct. 1	10465					Removal of pancreatic tissue weighing 21.2g. An elongated strip, the edge being removed, was left communicating with both ducts; its size is estimated as one fourth of the gland. Ramus pancreaticus inferior was small; ligated. Omental covering.
Oct. 2		A.M. 100^{3} Specimen (with vomitus)			Neg.	No defecation. Vomits water.
" 3		A.M. 101 (with diarrheal feces)	175		"	Lively. One defecation, partly solid and partly liquid. Retains water. Hungry.
" 4	9440	A.M. 101^{1}	220 (with feces)		"	Thin, dark diarrhea. Afternoon, allowed a little bread-and-meat.
" 5	9150	A.M. 101^{6}	375 (with feces)		"	Acts well, but has not eaten much.
" 7		Specimen			"	Doing well. Dark, liquid feces.
" 16	9540	A.M. 101^{6}	Specimen		"	
" 18			"		"	
" 19						In operation under ether, one fine wire loop (a strand from No. 3 picture wire) was passed loosely about portal vein, and ends left protruding from abdomen.
Oct. 20		A.M. 102^{2}				Lively. Retains water qs.
" 21		A.M. 102^{7}	120	1080	Neg.	Acts entirely well. In the morning was given a hearty meal of bread-and-meat mixture, which was eaten well. One small semi-solid defecation today. Large appetite. 5 P.M. fed glucose-milk and glucose-bread-and-meat mixture.
Oct. 22		A.M. 103^{1} (with diarrheal feces)	450		1.1%	Lively and hungry. Slight diarrhea. Fed bread-and-meat mixture sweetened heavily with glucose and cane-sugar.
" 23		(largely diarrheal feces)	160		Neg.	Fed milk, and bread-and-meat mixture, both sweetened with cane sugar.
" 24	9640	A.M. 102^{5} (with a little diarrheal feces)	310		0.9%	Has eaten rather poorly. Diarrhea. On roof for exercise. Fed bread-and-meat mixture with cane-sugar.
" 25	9220	A.M. 101^{4} (14 hour specimen)	450	1026	Neg.	Has eaten all feed. Lively. On roof for exercise.
" 26	8875	A.M. 102 (with diarrheal feces) (16 hour specimen)	280		"	Has eaten rather poorly. Moderate diarrhea.
" 27	8800	101^{6} (16 hour specimen)	75	1065	"	Has eaten rather poorly. Diarrhea.
" 28	8640	A.M. 102	310	1050	"	Has eaten all feed. Dark diarrhea.
" 29		(with a little feces)	340		"	
" 30	8900	A.M. 101	325	1028	"	Has eaten all feed. Feces soft, well digested. On roof for exercise.
" 31	9220	A.M. 102^{8} (18 hour specimen)	640	1020	"	Has eaten a very large feed of bread-and-meat. Feces moderate quantity, black, semi-solid. On roof for exercise.
Nov. 1	9200	A.M. 103^{2} (with a little diarrheal feces) (18 hour specimen)	100		"	Has eaten heavily of bread-and-meat. Slight diarrhea, black. Traction is made daily on wire surrounding portal vein.
" 2	9200	A.M. 102^{3} (24 hour specimen)	450	1046	Neg.	Has eaten less than usual. Black diarrhea. On roof for exercise.
" 3	9100	A.M. 101^{6} (with diarrheal feces) (18 hour specimen)	435		"	Feces partly soft, partly diarrheal, not bulky.
" 17		(18 hour specimen)	250	1034	"	
" 18			760	1020	"	

Date	Weight g.	Temp.	Urine			Treatment and Remarks.
			Quant. cc.	SpG.	Bene-dict	
Nov. 19			600	1016	Neg.	It sometimes appears as if long and frequent traction on wire about portal vein is productive of polyuria, but question is not definitely decided.
" 20	9600	A.M. 101^5	460	1017	"	Excellent condition. Today the first perfectly formed feces. In pulling wire, one end escaped, and the pull on the other end brought it out. Portal vein is therefore not obliterated.
" 21			530	1028	"	Diet changed from bread-and-meat mixture, to bread and soup.
" 22			405	1034	"	On roof for exercise.
" 23	(18 hour specimen)		320	1030	"	" " " "
" 24	9850	A.M. 101^1 (18 hour specimen)	100	1042	"	Sinus in abdomen completely healed.
" 27	9900	A.M. 100^8				Abdomen opened in the old scar and many adhesions, chiefly the result of the portal vein operation, were separated. Pancreas remnant was exposed and found healthy. Pancreatic tissue from the central portion was removed to the extent of 5.75g. weighed fragments, and smaller fragments resulting from scraping and sponging probably brought total removed to 6g. Largest remnant left was about main duct. A much smaller one remained about a smaller duct, and shreds of appreciable size, along pancreatico-duodenal vessels, communicating with no duct. A number of ligatures close to these vessels were required, and the trunks themselves were ligated close above the main remnant. No disturbance of inferior pancreatico-duodenal circulation. Remnants and the bare areas of duodenum were covered with omentum and the abdomen closed.
Nov. 29	9050	A.M. 99^5				Somewhat depressed. Refuses water. Hungry.
" 30			165 (First urine since operation)	1050	Neg.	Lively. Fed 200cc. milk.
Dec. 1	8600	A.M. 101^4 (passed before taking milk yesterday)	100	1050	Neg.	Fed some bones. Lively and hungry.
		(passed since taking milk yesterday)	10		12%	
" 2			270	1057	4%	Fed 500g. meat. Ate 350g.
" 3	8450	A.M. 101^9	310	1064	7.1%	Feces semi-solid, well digested. Fed 500g meat. On roof.
" 4	8320	(18 hour specimen)	255	1096	7.4%	Has eaten all feed. Feces soft, fairly well digested. Today fed 250g. meat; not very hungry.
" 5	8050		200	1068	6.4%	Yesterday's feed eaten. Fed 750g. meat.
" 6			530	1050	5.6%	All feed eaten. On roof for exercise. Rather weak. (Diabetic asthenia). Feces well digested, but moderate diarrhea. Fed 750g. meat.
" 7	8050	A.M. 102^5 (with diarrheal feces)	350		5%	Feed all eaten. Moderate diarrhea. On roof for exercise. Fed 750g. meat.
" 8	7920	A.M. 101^5 (with diarrheal feces) (18 hour specimen)	140		7.4%	About 150g. feed uneaten.

Abdomen was opened in the old scar and pancreas-remnant easily found, protected by its omental covering. A liver-edge adherent to duodenum caused a little difficulty. The main pancreatic duct was easily found and cut between ligatures. A ligature was also passed about the upper pole of this remnant where there is perhaps communication with a smaller duct. This remnant is thus probably cut off from all excreting passages, but further search was omitted in order to cause the least possible trauma. A smaller fragment above remains communicating with smaller duct. The remnant was re-covered as well as possible with omentum and the wound closed.

DOG 104 (Continued).

Date	Weight	Temp.	Urine			Treatment and Remarks.
			Quant. cc.	Sp.G.	Benedict	
Dec. 9			20	1100	2.6%	As lively as could be expected of a weak dog. Retains water qs.
" 10			180	1058	Neg.	Given 200cc. milk. Taken promptly.
" 11	7500	A.M. 100	180	1048	0.7%	No feces. Cheerful and hungry. Fed 1 kilo meat and pancreas.
" 12	7600	A.M. 101^6	310	1056	2.4%	Feces pasty. Has eaten 700g., including more pancreas than meat. Fed 800g. horsemeat without pancreas.
" 13	7820	A.M. 100^8	640	1050	1.8%	All feed eaten. Feces bulky, soft, rather poorly digested. Fed 1 kilo meat.
" 14	7610	A.M. 103^8	590	1051	4.5%	Lively and well-appearing. Has eaten 850g. out of yesterday's kilo. Feces soft, fair bulk and digestion. The fragment about the smaller duct evidently still communicates with bowel. Fed 900g. beef.
" 15	7360	A.M. 102^2	470	1060	5%	Has eaten little more than half feed. Fed 1 kilo beef.
" 16	7590	Diabetic odor noticed for first time.	450	1070	7.5%	Feed all eaten. Fed 1 kilo horsemeat. Feces semi-solid; medium bulk and digestion.
" 17		No diabetic odor.	910	1062	8.2%	Meat 250g. uneaten. Fed 1 kilo horsemeat. Feces bulky, semi-solid, imperfectly digested.
" 18		No diabetic odor	675	1064	12.1%	All meat eaten. Fed 1 kilo meat.
" 19	7610	A.M. 102^7	935	1045	5.6%	Meat 250g. uneaten. Feces bulky, but hard, perfectly formed and fairly digested. Fed 1 kilo meat.
" 20			730	1052	8%	On roof for exercise. Meat 100g. uneaten. Fed 1 kilo.
" 21	7480	Slight diabetic odor	940	1058	7.7%	

Feed all eaten. Not fed today. Dog is cheerful, but so weak he can hardly ascend stairs. Feces soft; digestion medium. Abdomen was opened in the old scar, and upper peritoneum found to be nothing but a mass of adhesions; liver, stomach, pancreas and intestine stuck fast together. The pancreas remnants and neighboring duodenum were finally exposed, and the large lower remnant found showing atrophic changes. The upper, smaller remnant is healthy and evidently secreting. This remnant was dissected entirely free from the duodenum, and in the process the smaller duct was found, and cut between ligatures. The circulation of the remnant was preserved intact, but that of the adjoining duodenum was sacrificed to dangerous extent, and gangrene of duodenum may result. A long difficult operation. Dog was removed from table decidedly weak, but in no immediate danger. Wakes up well from anaesthetic.

Dec. 22	Prior to yesterday's operation	150	1057	10.5%	In good condition except for weakness. Retains water qs.; no vomiting.
	Since yesterday's operation	110	1070	3.5%	
" 23	Post-mortem. (Chiefly or wholly feces and vomitus)	600		Neg.	Found dead. Autopsy shows gangrene of duodenum. Pancreas tissue is somewhat atrophic but with intact blood-supply. Its total weight is 8.1g. Other organs negative.

For microscopic findings see Chapter XII.

Male; Irish terrier mongrel, yellow, rough; medium flesh.

Date	Weight g.	Temp.	Urine			Treatment and Remarks.
			Quant. cc.	SpG.	Benedict	
Nov. 24	14360					Received. Has fasted two days.
Removal of pancreatic tissue weighing 23g. Remnant about main duct estimated at 5g. A ligature was passed about the remnant at a point near its middle, tightened so as to cut through the gland tissue and injure but probably not destroy the vessels and nerves in its grasp, and then removed. Ramus pancreaticus inferior ligated. Omental covering.						
Nov. 25		A.M. 100^4				Lively. Retains water.
" 26			175	1030	Neg.	" Feces very hard & dry.
(First urine since operation)						
" 27	13130	A.M. 102^2	215 (last evening)	1038	"	Fed 250cc. milk. No more feces.
			280 (this morning)	1032	"	
" 28	12840	A.M. 102^7	515	1030	"	Fed 200g. horsemeat; eaten greedily.
" 29			1020	1020	"	Drinks enormously. Fed 400g. horsemeat, eaten promptly.
" 30	12500	A.M. 102^7 (a litre or more additional urine thrown away).	450	1020	"	Feces firm. Fed 500g. meat, eaten promptly.
" 1	13180		1080	1022	Faint	Fed 750g. meat. Feces firm.
" 2			1425	1034	1.4%	Has eaten all feed. Fed 1 kilo meat.
" 3	13400	A.M. 101^4	1000	1035	0.48%	Has eaten all feed, and still hungry. Today fed 1400g. meat. Feces scanty, semi-solid.
" 4	12860		1325	1038	1.1%	Has left 500g. out of yesterday's 1400. Feces well-digested, partly solid, partly soft. Today fed 1 kilo meat.
" 5	13660		940	1030	Faint	All yesterday's feed eaten. Slight diarrhea. Fed 1400g. meat.
" 6			1490	1032	Neg.	Feed all eaten. Feces soft, well-digested. On roof for exercise. Fed 1200g.
" 7	13400	A.M. 100^5	465	1044	"	All feed eaten. On roof for exercise.
Abdomen opened in the old scar, and omental covering easily rolled back from pancreas remnant. Operation was for purpose of attempting to produce diabetes by breaking nerves to this remnant. Along the superior pancreaticoduodenal vessels, where blunt dissection had been done in the previous operation, the attempt to find nerves soon started several points of hemorrhage, resulting in double ligation of the entire bundle, and failure to identify any nerve fibres. Below the remnant, nerves were easily found and broken at two points, viz. one point along ramus duodenalis inferior, and one point along ramus pancreaticus inferior. The vessels themselves were not damaged, and the pancreas remnant was not disturbed. The omental covering was replaced, and the abdomen closed.						
Dec. 8			No urine			Retains water qs. Lively. Hungry.
" 9			225	1050	Neg.	Fed 250cc. milk.
" 10			670	1024	"	" 500g. meat, eaten promptly.
" 11	11700	A.M. 102	370	1040	"	On roof for exercise. Fed 1500g. meat.
" 12		(14 hour specimen)	435	1036	"	All feed eaten. Feces soft, well-digested. Fed 1500g. meat.
" 13	12800	A.M. 101^5	1620	1032	"	Feed all eaten. Feces soft, well-digested. Fed 1500g. meat.
" 14	12960		1100	1040	"	All feed eaten. Slight diarrhea. Fed 1500g. meat.
" 15	13750	A.M. 101^4	650	1043	"	All feed eaten. Not fed today. At 2.30 P.M., sugar-puncture performed under ether, two strokes being made.
" 16			920	1036	"	Dog is lively, but shows marked left hemiplegia. Given 1 kilo meat.
Total urine prior to puncture yesterday (when bladder was emptied) Albumin neg.						
			25 since puncture	1055	2.2%	
Albumin moderate.						
" 17			690	1058	2.6%	Feed all eaten. Fed 1500g. meat. No feces.
Albumin neg.						
" 18			475	1060	0.7%	About 350g. meat uneaten. Fed 1300g.

DOG 154 (Continued).

Date	Weight g.	Temp.	Urine			Treatment and Remarks.
			Quant. cc.	SpG.	Benedict	
Dec. 19	12800	A.M. 101^7	300 (with a little feces)		Neg.	560g. meat uneaten. Dog is cheerful, but still unable to stand, on account of left hemiplegia. No salivation. Fed 1 kilo meat, but shows no appetite today. Tied out on back in warm room from 4 P.M. to 7.30 P.M. Worries very little and shows no salivation. Considerable urine lost while tied; all negative to Benedict test. Very thirsty on returning to cage.
			100 (with feces) (passed before tying)		Neg.	
			110 (passed since tying)	1050	Neg.	
" 20			No urine			100g. meat uneaten. Fed 1250g. meat, eaten promptly.
" 21			880	1050	Neg.	Fed 1500g. meat.
" 22	12800	A.M. 102^5	350	1054	"	600g. meat uneaten. Dog is beginning to stand and walk, but very drunkenly. Is very cheerful. Feces hard, well digested.
Abdomen opened in the old scar, and pancreas remnant found in good condition. It is smoothly covered by omentum everywhere except at upper pole, where liver is adherent. These adhesions were separated, and from this pole was removed pancreas-tissue weighing 0.95g. Omental covering was then replaced and abdomen closed.						
Dec. 23			180 Urine since operation.	1055	Neg.	Lively. Retains water qs.
" 24			300	1050	Neg.	Fed 200g. meat, eaten promptly.
" 25	Specimen (with spilled water)					Fed 1500g. meat.
" 26	12400 (About an equal quantity lost)		420	1050	0.6%	250g. meat uneaten. Fed 1200g. meat.
" 27			625	1052	4.6%	Feed barely eaten. Fed 1200g. meat.
" 28			1500	1050	8.3%	All feed eaten. Feces soft-solid, well-digested. Fed 1200g. meat.
" 29			1090	1050	4.8%	Not fed today.
Abdomen opened by incision well over in right flank, and pancreas remnant easily found, smoothly covered by omentum. After somewhat troublesome dissection, owing to bleeding adhesions between pancreas and duodenum, the duct was found and doubly ligated, but not cut. Omental covering replaced and abdomen closed.						
Dec. 30			320 (Prior to operation yesterday)	1060	4.8%	No urine since operation. Lively. Retains water qs. Hungry.
" 31			240	1058	5%	Fed 350g. meat, eaten ravenously. Evening, an additional 350g., also eaten greedily.
Jan. 1	10950	A.M. 102	700	1055	5%	Fed 750g. meat, eaten immediately. Evening, fed another 750g.
" 2	10950	A.M. 102^8	960	1060	7.6%	330g. meat uneaten. Fed 1200g. meat. Slight diarrhea today.
" 3	11200	A.M. 101	1870 (with a little diarrheal feces)		8%	All feed eaten. Semi-liquid diarrhea. Digestion poor. Fed 1400g. meat.
" 4	11360	A.M. 101^8	1050 (with diarrheal feces)		9.1%	50g. meat uneaten. Fed 1100g. meat and 100g. pancreas.
" 5	11370	A.M. 101^4	1970	1052	12.2%	All feed eaten. Fed 1100g. meat and 200g. pancreas.
" 6	11650	A.M. 101^2	1165	1060	9.2%	Feces soft. All yesterday's feed eaten. Fed the same today: eats pancreas first.
" 7	11180	A.M. 100^2	2050	1050	11.2%	All feed eaten. Feces pasty. Fed 1400g. meat.
" 8	11370	A.M. 101^8	1500	1054	11.2%	All feed eaten. Feces soft. Fed 1500g. meat.
" 9	10750	A.M. 102^8	1575	1060	10.4%	Diarrhea of poorly digested, black, semi-liquid material. Starvation begun.
" 10	10690	A.M. 100^8	600	1055	10.4%	
" 11	10330	A.M. 101^6	155	1058	5.4%	

Date	Weight g.	Temp.	Urine			Treatment and Remarks.
			Quant. cc.	Sp.G.	Benedict	
Jan. 12	9930	P.M. 101	85 230	1046 1020	1.2% 1.5%	Yesterday's and today's urine of this dog are clear amber when passed, but after standing some hours turn almost black.
" 13	9860	A.M. 101^4	155	1038	4.3%	
" 14			50	1060	8%	
" 15	9460	A.M. 101^4	50	1060	9.1%	Urine continues to be clear amber while fresh, changing gradually to almost black.
" 16	9000	A.M. 101	230	1066	very heavy	Urine thrown away by mistake before titration.
" 17			140	1092	9.1%	
" 18	8450	A.M. 100	235	1070	15.2%	
" 19	8250	A.M. 100^4	275	1080	14.6%	
" 20	8010	A.M. 100^8	195	1060	10.4%	Fed 200g. meat and 200g. pancreas. Afternoon given another similar meal. All eaten ravenously.
" 21			1025	1058	7.06%	Fed 800g. meat and 400g. pancreas.
" 22	8770	A.M. 101^2	805	1064	14.5%	150g. meat uneaten. Fed 500g. meat and 300g. pancreas.
" 23	8730	A.M. 100^8	690	1060	8.79%	110g. pancreas and 230g. meat uneaten. Fed 400g. meat and 300g. pancreas.
" 24	8680	A.M. 100^1	915	1056	6%	All feed eaten. Fed 250g.meat and 200g. pancreas.
" 25	8320	A.M. 100^4	820	1052	5.2%	All feed eaten. Fed 600g. meat and 400g. pancreas.
" 26	8020		710	1060	7.3%	All feed eaten. Given away for observation in another department of this school.
" 31	Death and autopsy.					

Body greatly emaciated, as in simple starvation: no sign of body-fat. Gross appearance of organs negative. Pancreas remnant surrounded by adhesions, but none appear to cause any obstruction of bowel. The remnant weighs 4.85g. Its tissue is of normal appearance and consistency, and the duct is fully patent. Even the two Pegenstecher ligatures are absent, and the only remaining effect from them is possibly that the duct is larger and its walls collapse less easily than ordinary, as if from previous dilatation or inflammation.

In the floor of the fourth ventricle, in the optimum sugar area of its lower portion, are seen three punctures one in front of the other, all accurately in the middle line.

For microscopic findings see Chapter XXI.

DOG 155.

Male; mongrel, brindle, age two years; medium flesh.

Date	Weight g.	Temp.	Urine			Treatment and Remarks.
			Quant. cc.	Sp.G.	Benedict	
Nov. 24	12550					Received. Has fasted two days.
Removal of pancreatic tissue weighing 17.7g. Remnant about main duct estimated at 3.5g. maximum. Ramus pancreaticus inferior is represented only by a small branch; ligated. Other vessels spared. Omental covering.						
Nov. 25		A.M. 100^4				Lively.
" 26			P.M. 240 (First urine since operation)	1058	Neg.	Lively. Retains water qs. No feces.
" 27	11500	A.M. 100^3	515	1015	Neg.	Fed half pint of milk. No feces.
" 28	11360	A.M. 101^5	290	1024	1%	Fed 200g. horsemeat; eaten greedily.
" 29			370 (with a little diarrheal feces)		3.3%	Fed 400g. horsemeat; only part eaten.
" 30	10960	A.M. 101^4	690	1034	2.9%	Has left about 50g. of yesterday's meat uneaten. Today fed 500g. meat; eats only a little. Slight diarrhea.
Dec. 1	11020	A.M. 100^9	525	1050	6.1%	Left 75g. out of yesterday's 500g. Fed 600g. meat.
" 2	11185	A.M. 101^5	555	1044	4.1%	Has eaten all yesterday's 600g. Fed 1 kilo meat.
" 3	11000	A.M. 101	900	1043	4.6%	Left 200g out of yesterday's kilo. Today fed 1 kilo meat. Slight diarrhea.
" 4	10400		1030	1044	7.8%	Has left 450g. uneaten. Profuse diarrhea Today fed 1 kilo meat.
" 5	10860	A.M. 100^7	695 (before operation)	1042	4.3%	Ate all yesterday's feed. Diarrhea.
			280 (at close of operation)	1036	2.9%	The abdomen was opened in the old scar, and the pancreas remnant found in good condition. It was treated by anchoring the duodenum against the parietal peritoneum, and partly rotating it so as to bring the pancreas forward. The presenting margin of the pancreas was then sutured to the skin, so that when the wound was closed, the pancreas remnant was inclosed in the abdominal wall. The dog was not well suited for this operation, and undue strain and trauma in and about the pancreas remnant were necessary to accomplish it. Also a ligature was passed about a portion of the pancreas remnant, so as to spare the vascular supply, but supposedly to cut off approximately the upper third of the remnant from communication with the duct. Where this ligature bit through the gland tissue, a tab of omentum was drawn between the two portions.
			60	1052	6.6%	
Dec. 6			95	1090	5.8%	Very lively, but vomited water. Not hungry.
" 7			40	1098	5.6%	Lively. Retains water qs.
" 8	9950	A.M. 102	295	1044	3.6%	Fed 250g. meat, eaten promptly.
" 9			450	1034	3.8%	Fed 500g meat. Has vomited a little of yesterday's meat.
" 10			650 (with diarrheal feces)		very heavy	250g. meat uneaten out of yesterday's 500g. Fed 500g. today.
" 11	9460	A.M. 101^5	835	1030	2.5%	250g. meat uneaten. Lively. On roof for exercise. Fed 500g.
" 12			650 (14 hour specimen)	1030	2.5%	All feed eaten except 25g. Fed 500g. meat.
" 13	9200	A.M. 101^1	550	1030	2.9%	Moderate diarrhea. 225g. meat uneaten. Fed 500g.
" 14	8980		960	1034	4%	100g. meat uneaten. Slight diarrhea. Fed 500g. meat. There is a plainly palpable mass in the abdominal scar, apparently the pancreas remnant.

DOG 155 (Continued).

Date	Weight G.	Temp.	Urine			Treatment and Remarks.
			Quant. cc.	Sp.G.	Benedict	
Dec. 15			1060 (with diarrheal feces)		2.8%	All feed eaten. Fed 500g. meat.
" 16	8910		750 (with diarrheal feces)		2.9%	All feed eaten. Fed 500g. meat
" 17			400	1026	3.3%	Has eaten only 250g. Fed 500g meat.
" 18			580	1042	4.6%	All eaten. Fed 500g.meat.
" 19	8760	A.M. 101.3	670	1040	6%	Feed all eaten. Moderate diarrhea. Fed 800g. meat.
" 20			1320	1036	4.8%	On roof for exercise. Feed all eaten (a marked increase of appetite). Fed 1 kilo.
" 21	9400		970	1040	9.9%	175g. meat uneaten. Fed 1 kilo.
" 22			1560	1040	7.8%	250g. meat uneaten. Fed 900g.
" 23	9070		1625 (with a little vomitus and feces)		9%	Feed all eaten, but a portion vomited. Slight diarrhea. Not fed today.

Abdomen opened in the old scar, and pancreas remnant dissected free from abdominal wall. The duct was located with a minimum of dissection, though a slight laceration of pancreas tissue was unavoidable in so doing. The duct was cut between ligatures, and all further dissection avoided.

The remnant was covered with omentum and with the duodenum dropped free into the peritoneal cavity. The wound was then closed as usual.

Dec. 24			235 (prior to operation yesterday)	1035	5.8%	Dog lively, but vomits.
			370 (since operation yesterday)	1065	10%	
" 25	Specimen with feces (postmortem)				Heavy	Found dead. Autopsy shows general peritonitis. Pancreas remnant healthy; weight is 6.75g. Other organs negative.

For microscopic findings see Chapter XXI.

DOG 166.

Male; mongrel, brown; age 2 years. Good condition.

Date	Weight g.	Temp.	Urine			Treatment and Remarks.
			Quant. cc.	Sp.G.	Benedict	
Dec. 11	11960					Received. Has fasted 24 hours.
" 12						Removal of pancreatic tissue weighing 17.3g. Remnant about main duct estimated at 5g. Ramus pancreaticus inferior was absent. Ramus duodenalis inferior supplied pancreas by side-branches. About the portal vein was passed a single ligature of Pagenstecher, which was tied so as to reduce the vein to a fraction of its size at this point, but not entirely occlude it. Also, a single loop of fine wire was passed about portal vein, but not tied; similarly a double loop of heaviest surgical silk, not tied. Ends of all these ligatures protruded from abdomen near upper angle of wound. Omentum was draped so as to cover the duodenum and pancreas remnant, and also surround the ligatures.
Dec. 13			100	1060	Neg.	Fairly cheerful, but vomits water persistently. (First urine since operation.)
" 14			100	1060	"	Very lively, but still vomits water. Later retains some.
" 15	10400	A.M. 101^8	No urine			Still lively, but had vomiting and one diarrheal defecation last night, and today still vomits water. Diarrhea continues today.
						Dog shows the need of water, so at 4.30 P.M., between shoulders, was given subcutaneous injection of 500cc. 0.85% NaCl solution containing 20g. commercial glucose.
Dec. 16			275	1044	3.8%	Lively. Retains water qs.
" 17			260	1040	2.3%	Given 150cc. milk. Almost no appetite.
" 18			265	1050	2.7%	Milk all taken. Fed 250g. meat.
" 19	10225	A.M. 101^5	315	1052	7.1%	All feed eaten. Ligature-ends protected by braiding with wire. Fed 500g. meat. Still listless, with little show of appetite.
" 20			675	1040	6.1%	Meat 100g. uneaten. Fed 500g.
" 21			620	1042	7.5%	Meat 250g. uneaten. Fed 350g.
" 22			750	1032	5.0%	Meat 175g. uneaten. Feces semi-solid, fairly well digested. On roof for exercise. Fed 250g. meat.
" 23			750 (18 hour specimen)	1036	6.4%	All eaten. Fed 250g.
" 24			750	1042	7.5%	Meat 25g. uneaten. Fed 250g.
" 25			925	1042	10.4%	All eaten. Fed 350g.
" 26	8900	A.M. 102^7	950	1040	5.2%	Meat 100g. uneaten. Today, by a slight pull on the ligatures, they came out with loops intact, proving portal vein to be now obliterated. Feces beginning to be well formed. Fed 360g. meat.
" 27			1350	1034	7.3%	All feed eaten. Fed 400g. meat.
" 28	8600	A.M. 103^6	920	1040	7.8%	Meat 170g. uneaten. Fed 300g. For past week or more; dog has shown weakness. Feces soft, reasonably well digested.
" 29			800	1040	5.6%	Meat 25g. uneaten. Feces soft-solid. Fed 300g. meat.
" 30			290 (Postmortem.)	1060	6.5%	Found dead. Very little of yesterday's feed eaten.

Autopsy shows that the fine wire passed about the portal vein had been broken off (probably by the dog), so that the ends no longer protruded from the abdomen. This wire therefore did not come out when the other ligatures came, and remained inside, finally causing general peritonitis and death. The pancreas remnant was healthy, and weighed 10.9g. The portal vein was obliterated where ligated at the operation. Other organs negative.

For microscopic findings see Chapter XXI.

DOG 167.

Male; mongrel, dark-brown; age 4 years. Plump.

Date	Weight g.	Temp.	Urine			Treatment and Remarks.
			Quant. cc.	SpG.	Benedict	
Dec. 11	17600					Received. Has fasted 24 hours.
Removal of pancreatic tissue weighing 34.4g. Remnant about main duct estimated at 6.5g. About portal vein was passed a loop of heaviest surgical silk and another of fine wire. The ends of both were left protruding near upper angle of wound. The omentum was draped so as to cover duodenum and pancreas remnant, and also to surround the silk & wire.						
Dec. 12						Lively. Retains water. One large liquid defecation.
" 13			455	1045	Neg.	
(First urine since operation)						
" 14			500	1027	"	Lively and hungry.
" 15	16740	A.M. 101^6	480	1020	"	Fed 250g. minced horsemeat.
" 16			435	1030	"	Acts somewhat depressed. Has eaten less than half his feed. Feces soft, well-digested. Fed 350g. meat. Dog has been meddling with ends of ligatures, which therefore today were protected by braiding with wire. Diarrhea.
" 17			700	1020	"	Has eaten 100g. meat. Fed 250g.
" 18			575		"	Fed all eaten Fed 400g. meat.
" 19	15500	A.M. 101^6	360	1020	"	" " " " 800g. " Still rather listless, with little show of appetite. Dog is beginning to drink in notably abnormal quantity.
" 20			850	1018	"	500g. meat uneaten. Fed 500g. meat.
" 21			1290	1022	"	Feed all eaten. Fed 500g. meat.
" 22			1200	1018	"	200g. meat uneaten. Feces semiliquid, improving. On roof for exercise. Fed 350g. meat.
" 23	15200		450	1020	"	150g. meat uneaten. Fed 350g.
(18 hour specimen)						
" 24			1100	1020	"	100g. meat uneaten. Fed 350g.
" 25	14840		1170	1012	"	125g. " " Slight diarrhea. Diet changed to bread-and-meat mixture.
" 26	15070	A.M. 104^2	650	1017	"	Lively. Has eaten fairly. Feces soft. Bread-and-meat diet continued.
	Later		585	1010	"	
" 27	14625		550	1007	"	Has eaten rather poorly. Today, by slight traction on the ligatures, they came out intact, thus showing that portal vein is obliterated. Same diet continued.
(some urine lost)						
" 28	14600	A.M. 103^6	610	1014	"	Fairly lively. Eats bread-and-meat in fair quantity. Feces soft-solid, well digested.
" 29			900	1018	"	Has eaten poorly. Same diet.
" 30			295	1020	"	
(14 hour specimen)						
" 31			880	1015	"	
Jan. 1	14875	A.M. 104^6	725	1011	"	Bread-and-meat diet continued. Appetite and liveliness have been fair. Right hind leg is today swollen and lame, either from some injury the dog has done himself, or from unknown cause. Fed 1 kilo meat, but dog is sick and shows no appetite.
Jan. 2			1550	1018	"	Has eaten nothing. Not fed.
" 3	14270	A.M. 104^6	885	1010	"	Some appetite; fed meat. Enormous abscess of unknown origin broken on right hind leg.
" 4			1100	1015	"	Has eaten what was given. Feed increased.
" 5			1750	1020	"	Has eaten his feed, but is thin and sick. Left leg has swelled recently exactly as right did. Today fluctuation is evident; and a knife-opening at a place corresponding to the spontaneous pointing on the right leg (outer surface midway between knee and ankle) brings an abundant flow of pus. This leads to assumption that abscesses are metastatic from some focus, probably about the liver.
Jan. 6			1750		"	Eating better, but also growing weaker. Right hind leg too lame to use. Diarrhea.
(with diarrheal feces)						
" 7			1425		"	
(with diarrheal feces)						
" 8	12700	102	800		"	
(with diarrheal feces)						

Date	Weight g.	Temp.	Urine			Treatment and Remarks.
			Quant. cc.	SpG.	Benedict	
Jan. 9	12370	A.M. 99.5 (with diarrheal feces)	1220		Neg.	Fed meat and bread scraps, containing sugar. Eats better. Diarrhea continues.
" 10	13790	A.M. 99.6	850		7.3%	Fed meat and bread-scraps containing sugar. Eats heartily.
" 11			815	1040	6.6%	Fed standard bread-and-meat mixture. Feces are becoming formed and well digested.
" 12	14250		1500	1022	3.65%	Left hind leg practically well. Right hind leg just beginning to be used; has been completely disabled heretofore. Dog acts well and eats heartily. Not fed today.

Abdomen was opened in the old scar, and pancreas and duodenum were found smoothly covered by omentum, and free from other adhesions. Adhesions (chiefly omentum) in portal fissure were not disturbed. The pancreas-remnant was about the same size as left at the former operation, and its tissue appeared normal to sight and touch. From edge of pancreas-remnant farthest from duodenum was removed tissue weighing 2.1g. In removing the tissue, the venous hemorrhage was apparently more abundant and more persistent than usual. The omental covering was replaced and the abdomen closed.

" 13			320 (before operation) 220 (since operation)	1020	Neg. "	Very lively. Retains water qs.
" 14			290	1025	"	Fed 200g. meat, eaten promptly.
" 15	13180	A.M. 101.8	200	1024	"	Fed 800g. meat
" 16			765	1032	1.9%	Fed 600g. meat. About 25g. meat left from yesterday.
" 17			1075	1032	2.9%	All feed eaten. Fed 800g. meat.
" 18	13070	A.M. 102.8	1150	1030	5.6%	" " " " 900g. " The infected right hind leg has been healing rapidly (notwithstanding glycosuria) and is now almost well. On roof for exercise.
" 19			880	1028	4%	200g. meat uneaten. Fed 600g. meat.
" 20	13440	A.M. 101.2	925	1025	1.8%	30g. " " " " " Diarrhea.
" 21			1650	1034	3.4%	All feed eaten " 800g. "
" 22			1075	1040	4.86%	150g. meat uneaten " 600g. "
" 23	13080	A.M. 100.4	1135	1036	4.29%	All feed eaten. Fed 600g. meat.
" 24			1825	1028	3.3%	" " " " 800g. "
" 25	12850	A.M. 102	1055	1040	4.5%	" " " " " "
" 26			1380	1034	5.4%	" " " Given away for observation in another department.
Feb. 16	8500					

Received, after period spent in another laboratory. Very weak; can barely walk. Has been on diet of dog-bread and milk, and has fasted for the past 24 hours. Today given water by tube to increase urine.

Feb. 17			410	1021	4.8%	At 5.30 P.M., fed 700g. meat.
" 18	9060		558	1033	6.5%	One defecation, well formed and digested. Fed 1 kilo horsemeat.
" 19	8980		770	1044	3.6%	200g. meat uneaten. Fed 1 kilo.
" 20	9000		950 (in pan) 204 (in bladder)	1060 1058	5.1% 8.1%	Has left 200g. meat from yesterday. Very weak: therefore killed by chloroform.

Autopsy shows extremely emaciated dog, with purulent eyes and nose (not distemper) and chronic ulcers still remaining at sites of former abscesses on hind legs. Thyroid and parathyroids appear normal. Heart and lungs entirely normal. Abdomen contains a few adhesions, but they cause no obstruction or derangement of viscera. Liver is very large and fatty. Portal vein is replaced by a band of scar-tissue at point of former ligature, and is patent on both sides of the band. Pancreas remnant is guessed to weigh between 4 and 6g. It is an elongated oval mass beside the duodenum, and its tissue appears normal. Spleen is of normal size, and a trifle dark in color. Kidneys are wet, rather soft, and markedly fatty. Adrenals normal. Testes are small, otherwise normal.

For microscopic findings see Chapter XXI.

DOG 173.

Male; mongrel, brown; age 3 years. Medium flesh.

Date	Weight g.	Temp.	Urine			Treatment and Remarks.
			Quant. cc.	SpG.	Benedict	
Dec. 20	10500					Received. Has fasted 24 hours. Removal of pancreatic tissue weighing 18.9g. Remnant about main duct estimated at 1.8g. Duct cut between ligatures, and remnant separated completely from duodenum. Circulation of remnant injured somewhat, but not dangerously. Ramus pancreaticus inferior ligated; other large branches all spared. Operation decidedly rough. Omental covering.
" 21			120	1058	Doubtful	Depressed. Retains water.
" 22					Neg.	A little livelier. Vomited a little during night. No feces.
" 23			265	1042	0.9%	
" 24			750	1010	Neg.	Given 250cc. milk, taken promptly. One defecation, dry & formed.
" 25	9400		190		"	Diarrhea. Diet of bread-and-meat mixture begun.
" 26			550	1046	4.7%	All feed eaten. Profuse diarrhea. Bread-and-meat continued.
" 27	9000		450		Heavy	All feed eaten. Diarrhea. Fed 700g horsemeat.
" 28	9240		300		Faint	All feed eaten. Diarrhea diminishing, but digestion poor. Fed 800g. meat.
" 29	9400		240		Neg.	100g. meat uneaten. Diarrhea diminishing. Fed 600g. meat and 100g. pancreas.
" 30			370		Faint	100g. meat uneaten. Fed 600g. meat and 100g. pancreas.
" 31			445	1058	Slight	Feed barely eaten. Fed 500g. meat and 100g. pancreas. Dog tends to eat meat and leave pancreas.
Jan. 1	9430	A.M. 100	460		"	Fed 200g. pancreas and 500g. meat.
" 2	9620	A.M. 100^6	320	1054	1.7%	Fed 400g. meat and 300g. pancreas.
" 3	10000	A.M. 99^8	335	1054	Faint	All feed eaten. Today fed 700g. pancreas.
" 4	10010	A.M. 100	300	1066	Neg.	All feed eaten. Fed bread-and-meat mixture. Ate too heartily. Vomited.
" 5	9260	A.M. 101	1600 (with vomitus)		Heavy	Fed bread-and-meat mixture, and 100g pancreas.
" 6			585	1034	"	Fed like yesterday. Feces soft. Eats only the bread-and-meat, till finally hungry enough to take pancreas.
" 7	9590		1850 (with feces)		"	Diarrhea. Fed 600g. meat and 100g. pancreas.
" 8	9780	A.M. 100^6	240	1040	Neg.	All feed eaten. Fed 350g. meat and 350g. pancreas.
" 9			455	1038	"	All feed eaten. Fed 700g. pancreas. Remainder uneaten at 5 P.M. fed forcibly.
" 10	9950	A.M. 101	490	1040	"	Vomited part of pancreas. Feces pasty. Not fed today.

Abdomen opened in the old scar, and pancreas remnant found partly covered by omentum, and partly by a couple of coils of adherent intestine. It was liberated enough to define accurately its size and boundaries, and then bisected as exactly as possible, one half removed and the other left in situ, uninjured except for ligature of one small vessel supplying it. The piece removed weighed 1.65g. By trimming, connective tissue and adherent omentum weighing 0.65g. was removed, leaving the actual pancreatic fragment weighing exactly 1g. On cutting, this piece is found to be obviously atrophic, the normal tissue becoming replaced by fibrous formation and dilated ducts. One pea-size retention cyst was encountered during today's operation, and drained.

Dog recovered quickly from anaesthetic, showing very little sign of depression.

DOG 173 (Continued).

Date	Weight	Temp.	Urine			Treatment and Remarks.
			Quant. cc.	Sp.G.	Benedict	
Jan. 11			150	1028	1.6%	Lively. Retains water qs. The first urine specimen here recorded was passed within half an hour after operation. Much of it was in bladder prior to operation, as palpation showed. The percentage of sugar is therefore somewhat surprising.
(A later specimen, with considerable vomitus)			160		1.3%	
" 12	9050	A.M. 101^{8}	125	1034	Neg.	Fed 200g. meat and 200g. pancreas: all eaten.
" 13			265	1038	"	Fed like yesterday. Meat eaten voluntarily, pancreas fed forcibly.
" 14			285	1050	"	Fed like yesterday.
" 15	8920	A.M. 101^{6}	195	1050	"	All feed eaten. Fed 400g. meat and 200g. pancreas.
" 16	9000		250	1046	"	All feed eaten. Fed 400g. meat and 200g. pancreas.
" 17			660	1028	"	All feed eaten. Fed 500g. meat and 200g. pancreas.
" 18	8920	A.M. 101^{6}	400		"	275g. meat uneaten. Fed 300g. meat and 300g. pancreas. Has little appetite today. On roof for exercise.
" 19			120	1050	"	160g. pancreas and 180g. meat uneaten. Fed 400g. meat.
" 20	8700		160	1044	"	All feed eaten. Feces formed, but bulky and very poorly digested. Fed bread-and-meat mixture.
" 21			625	1046	"	Has eaten well. Bread-and-meat diet continued.
" 22			350	1022	"	Has eaten poorly. Fed bread-and-meat mixture, also 200g. pancreas.
" 23	8980	A.M. 101^{6}	300	1032	"	95g. pancreas uneaten. Fed bread-and-meat mixture and 200g. pancreas.
" 24			240	1032	"	60g. pancreas uneaten. Fed like yesterday.
" 25	8900	A.M. 101^{6}	410	1036	1.14%	All feed eaten.

Not fed today. From 3 to 6 P.M., was used in dog-surgery class for entero-enterostomy by students. Autopsy performed at 6, while still breathing. All apparently normal, except adhesions about pancreas remnant, which is markedly atrophic. There is no communication with bowel.

For microscopic findings see Chapter XXI.

Male; Boston terrier, dark brindle, age 1½ years; medium flesh.

Date	Weight g.	Temp.	Urine Quant. cc.	Urine Spg.	Urine Benedict	Treatment and Remarks.
Dec. 28	7950					Received. Has fasted since yesterday.
Through incision to left of left Rectus, removed pancreatic tissue weighing 23.6g. Remnant about main duct estimated at 3.2g. Ramus pancreaticus inferior ligated; other trunks uninjured. Omental covering.						
Dec. 29						Lively. Retains water qs.
" 30			80 (with vomitus)		Neg.	
			20 (clear urine)	1052	Faint	
" 31			115	1040	"	Given 300cc. milk, taken promptly.
Jan. 1	6900	A.M. 102.3	310	1008	Heavy	Fed 500g. meat, eaten greedily. First defecation, soft-solid, well digested.
			75	1030	Faint	
" 2			230	1062	3.7%	Fed 1 kilo meat, and some milk. Very lively.
" 3	7240	A.M. 103.6	325	1059	6%	210g. meat uneaten yesterday. Fed 700g. meat today. Lively. Diarrhea.
" 4	6960	A.M. 102.6	325 (largely diarrheal feces)		Faint	480g. meat uneaten yesterday. Fed sour milk, also bread-and-meat today. On roof for exercise.
			45 (pure urine)	1045	Doubtful	
" 5	6850	A.M. 101.8	250 (18 hour specimen)	1063	Heavy	All feed eaten yesterday. Fed bread-and-meat mixture.
" 6			425	1065	Heavy	Very lively. Eats well. Feces soft. Bread-and-meat diet continued.
" 7			270	1076	"	ditto.
" 8	7390	A.M. 101.8	430	1064	18.2%	Diet of bread-and-meat continued.
" 9	7460	A.M. 102.4	485	1080	10.4%	Fed 600g. meat.
" 10			310	1066	4.8%	All fed eaten. Fed 700g. meat. Very lively.
" 11	7560	A.M. 102.6	280	1072	Faint	Not fed today. Feces well formed and well digested.
Abdomen opened by incision to right of right Rectus, and found entirely free from adhesions, except the smooth covering of the pancreas-remnant by omentum. This omental covering was easily rolled back; and from the pancreas-edge farthest from the duodenum was removed tissue weighing 0.56g. The remnant looked about the same size as when left at former operation, and its tissue appeared entirely normal to sight and touch. Omental covering was replaced and abdomen closed.						
Jan. 12			55	1064	1.7%	First urine passed a few minutes after operation.
			45	1050	1.2%	Second urine passed this morning.
" 13			95	1038	very faint	Very lively. Retains water qs. Not fed.
" 14			40	1084	Neg.	" "
" 15	6660	A.M. 101.8	25	1078	"	Fed 500g. meat, eaten promptly.
" 16			180	1065	"	Fed 600g. meat.
" 17	7200	101.8	150	1080	"	225g. meat uneaten.
Abdomen opened in the old left-side scar, and few peritoneal adhesions found. From margin of pancreas remnant was removed by piecemeal tissue weighing 0.6g. A short, easy operation. Omental covering was replaced and abdomen closed.						
Jan. 18			65 (before operation)	1040	Neg.	Lively. Retains water qs.
			150 (since operation)	1022	Neg.	
" 19			105	1034	Neg.	Fed 400g. meat. Ravenous appetite
" 20	6560	A.M. 102.6	225	1058	4%	Fed 800g. meat. Very lively, and eats all feed promptly.
" 21			375	1088	7.2%	Fed 400g. meat. Slight diarrhea. All feed eaten by evening.
" 22	6770	A.M. 102	455	1056	6.46%	Not fed today. Pancreatic duct was cut between ligatures; an easy operation, with little trauma to pancreas.

DOG 176 (Continued).

Date	Weight g.	Temp.	Urine			Treatment and Remarks
			Quant. cc.	Spg.	Benedict	
Jan. 23			20 (before operation)	1048	1.4%	Very lively. Retains water qs. Starvation is to continue till further notice.
			75 (since operation)	1064	1.46%	
" 24			145	1026	Neg.	
" 25	6160	A.M. 100^6	55	1050	Faint	
" 26			22	1112	"	
" 27	5840	A.M. 100^2	20	1120	Neg.	
" 28	5700		35	1070	"	Lively. Fast broken by feeding 50g. beef-pancreas, eaten eagerly.
" 29	5620		74	1052	"	Fed 50g. pancreas and 50g. beef-heart.
" 30	5560		60	1064	"	Fed 75g. pancreas and 75g. beef-heart. Slight diarrhea, black.
" 31	5470		80	1060	"	Fed 100g. pancreas and 100g. beef-heart.
Feb. 1	5475		60	1080	"	Fed 100g. pancreas and 100g. beef-heart. Very lively and active.
" 2	5490		150	1051	"	Fed 100g. pancreas and 100g. beef-heart. Slight diarrhea.
" 3	5610		60	1076	"	Same diet as yesterday.
" 4	5620		116	1053	"	" " " " " Feces well formed, scanty, well digested.
" 5	5620		134	1053	"	Same diet.
" 6	5625		55	1085	"	Fed 100g. pancreas and 120g. beef-heart.
" 7	5655		44	1100	"	ditto.
" 8	5770		30	1114	"	ditto.
" 9	5810		34	1120	"	ditto.
" 10	5865		22	1160	"	Fed 120g. beef-heart. Remarkable oliguria; never albuminuria.
" 11	5785		40	1088	"	Fed 120g. beef-heart and 100g. pancreas.
" 12	5810		44	1100	"	ditto.
" 13	5845		50	1092	"	Feed omitted by mistake.
" 14	5620		40	1080	"	Fed 100g. pancreas and 120g. beef-heart. Always eaten promptly.
" 15	5685		32	1120	"	Not fed.
" 16			38	1078	"	Fed 100g. pancreas and 150g. beef-heart.
" 17	5625		28	1120	"	ditto.
" 18			100	1072	"	Fed 100g. pancreas and 150g. horsemeat
" 19			56	1086	"	ditto.
" 20	5940		120	1090	"	ditto.
" 21			100	1072	"	Given about half feed and a large bone.
" 22			170	1051	"	All eaten. Fed 100g. pancreas and 150g. horsemeat.
" 23	6350		500	1046	3.7%	Lively. All yesterday's feed eaten. Not fed today.

Feces are entirely changed in character. Those passed during last night were black, copious, diarrheal, different from the paler, pasty, fairly abundant sort heretofore. But those of today are scanty, hard, black, normal looking, and perfectly digested.

Feb. 24			180	1062	Slight	Not fed.
" 25	6070		55	1084	Faint	Abdomen was opened in the old median scar, and the pancreas remnant found smoothly covered by omentum, and no other adhesions. Its size is the same as or a little larger than when last seen, and there is no appearance of atrophy. It was dissected free from the duodenum so far as possible without cutting off the blood supply of either, and what appeared to be a large duct was cut between ligatures. Two strips of omentum were then drawn through the space between pancreas and duodenum and secured by sutures, forming thus a double wall between them.
Feb. 26			20 (urine turns from amber to black on standing)		Faint	Lively, hungry. Retains water qs.
" 27			120	1022	Faint	Not fed.
" 28	5430		70	1042	Neg.	Fed 50g. pancreas, eaten very promptly.
" 29			45	1066	"	Fed 50g. pancreas and 50g. meat, eaten promptly.

Date	Weight g.	Temp.	Urine			Treatment and Remarks
			Quant. cc.	SpG.	Bene-dict	
Mar. 1		(urine scanty)			Neg.	Same diet.
" 2	5450		35	1092	"	All feed eaten. Lively. Fed 50g. pancreas and 100g. meat.
" 3					"	Fed 50g. pancreas and 50g. meat.
" 4					"	Same diet as yesterday.
" 5	5480				"	Fed 50g. pancreas and 200g. meat.
" 6	5570				"	ditto.
" 7	5700				"	ditto.
" 8					"	Same diet continues.
" 12					"	Feed all eaten daily. Fed 50g. pancreas and 250g. meat. Urine constantly sugar-free.
" 13						Fed like yesterday.
" 14	5605	Lively. Same diet. Today shows slight glycosuria.				
" 15		" " "				
" 17	6000	All feed eaten yesterday. 300g. meat and 50g. pancreas.				
" 19	6325	Very lively. Moderate glycosuria. Same diet as yesterday.				
" 20	6180	Fed 300g. meat and 50g. pancreas. All feed eaten.				
" 21		" " " " " " " " "				
" 24	6150	" " " " " " " " " Heavy glycosuria.				
" 25		" " " " " " " " "				
" 26		" " " " " " " " "				
" 27	6234	" " " " " " " " "				
" 28		" " " " " " " " "				
" 30	5910	" " " " " " " " "				
" 31		" " " " " " " " "				
Apr. 1		" " " " " " " " "				
" 2		" " " " " " " " "				
" 3		" " " " " " " " "				
" 4	6230	Very lively. Heavy glycosuria.				
" 5		Same diet. All feed eaten.				
" 10		" " " " "				
" 11		" " " " "				
" 13	Evening 6900	Very lively.				
" 16		Not fed today. Heavy glycosuria persists.				
" 17	6100	Diet of dog-bread only, begun.				
" 18		Yellow diarrhea; very poor digestion. 100g. pancreas added to dog-bread diet.				
" 30	5080	Has been on diet of only dog-bread for past week, without pancreas, and has lost weight rapidly. Intense glycosuria and polyuria.				
May 1		Killed by bleeding and autopsied at once. Body moderately emaciated, but still contains some fat. Thyroid, heart, lungs normal. Very few adhesions in peritoneum. Pancreas is atrophied down to a tiny nodule of about hazel-nut size, and on section this appears to be almost wholly fibrous tissue, with dilated ducts. There is no communication with the bowel. Liver moderately fatty. Kidneys unusually small, and blue with congestion. Spleen normal. Adrenals normal. For microscopic findings see Chapter XXI.				

DOG 177.

Male; mongrel, brown-brindle; age 2 years. Rather thin.

Date	Weight g.	Temp.	Urine			Treatment and Remarks.
			Quant. cc.	SpG.	Benedict	
Dec. 28	8225					Received. Has fasted over night. Removal of pancreatic tissue weighing 14.5g., through an incision to left of left Rectus. Remnant about main duct estimated at 1.4g. Ramus pancreaticus inferior ligated, other vessels spared. Omental covering.
" 29						Somewhat depressed. Vomits. Later retains water qs.
" 30						Well and lively.
" 31			180	1060	4.3%	Given about 150cc. milk, taken instantly.
Jan. 1	7370	A.M. 101^4	175	1064	7%	Fed 350g. meat, eaten promptly.
" 2			470	1070	10.4%	Fed 1 kilo of meat. Lively.
" 3	7190	A.M. 101^6	570		4.8%	390g. meat uneaten. Fed 600g. meat. Diarrhea.
" 4			370		6%	420g. meat uneaten. Fed 500g. meat. Diarrhea. On roof for exercise.
" 5	6480	A.M. 100^8	190		Heavy	All feed eaten. Fed 500g. meat. Diarrhea. At 5.30 P.M. the uneaten meat, weighing 300g., was removed from cage.
" 6	6400	A.M. 100^8	220		2.7%	This forenoon, abdomen opened by incision in right Rectus. Pancreatic duct easily found and cut between ligatures, without visibly breaking the surface of any pancreatic lobule. Omental covering replaced and abdomen closed.
" 7			85	1090	5%	Lively. Retains water qs.
" 8	5970	A.M. 101^8	120	1056	Faint	Fed 250g. horse-meat.
" 9	5900	A.M. 101^6	175	1065	Neg.	Feces scanty, poorly digested.
			120	1055	"	Fed 350g. meat, all eaten.
" 10	5660		135	1080	"	Feces bulky, formed, very poorly digested. Fed 350g. beef-heart and 50g. pancreas, eaten promptly.
" 11	5385		250	1060	"	Feces still very bulky and very poorly digested. Forenoon, fed 175g. beef-heart and 175g. pancreas. Afternoon, fed likewise 175g. beef-heart and 175g. pancreas. Dog has slight preference for pancreas. Is becoming thin and weak.
" 12	5240	A.M. 98^4	160		"	Fed 250g. beef-heart and 250g. pancreas.
			85	1070	"	Feces show the usual appearance for dogs of this sort.
" 13	5170	A.M. 101^2	200	1064	"	All feed eaten. Dog presents picture of impending death from starvation. Extremely emaciated, and so weak that he staggers and falls whenever he tries to walk. Yet feces show about the usual bulk and gross appearance as with other pancreas-fed dogs. Too weak today to eat voluntarily. At 11 A.M. injected between the shoulders with 50cc. solution containing 10g. levulose. Then fed forcibly 150g. pancreas. Toward evening vomited it all.
" 14	In pan		115	1084	2.4%	Found dead. Autopsy shows appearance of death from starvation. Viscera all normal in gross appearance.
In bladder at autopsy			40	1052	0.7%	

The pancreas remnant weighs 2.1g. It seems in perfect condition, but the communication with the bowel is entirely cut off. Not a sign of infection exists in it or in the whole peritoneum. The remnant is also smoothly covered by omentum, and other adhesions are entirely absent.

For microscopic findings see Chapter XXI.

DOG 178.

Female; mongrel, brindle, age 2 years; plump.

Date	Weight g.	Temp.	Urine			Treatment and Remarks.
			Quant. cc.	SpG.	Benedict.	
Dec. 29						Received. Has fasted 24 hours.
Through incision to left of left Rectus, removal of pancreatic tissue weighing 20.4g. Remnant about main duct estimated at 2.2g. Ramus pancreaticus inferior ligated; other stems spared. Omental covering.						
Dec. 30			180	1058	Faint	Lively. Retains water qs.
" 31						Given 150cc. milk, taken promptly.
Jan. 1	8560	A.M. 101^4	235	1048	Neg.	Fed 300g. meat, eaten promptly.
" 2			260	1062	5%	Fed 800g. meat. Lively.
" 3	8670	A.M. 101^2	1855	1023	2.9%	200g. meat uneaten. Fed 500g. meat today.
" 4	8280	A.M. 101^6	400 (with diarrheal feces)		6.5%	130g. meat uneaten. Fed 400g. meat today. Diarrhea. On roof for exercise.
" 5	8040	A.M. 100^6	275 (18 hour specimen) (with diarrheal feces)		Heavy	240g. meat uneaten. Diarrhea. Fed 200g. meat and 100g. pancreas.
" 6			530 (with diarrheal feces)		2.6%	155g. meat uneaten. Fed 300g. meat. Still hungry, therefore given a little bread-and-meat mixture, for benefit to digestion.
" 7			405	1055	5%	Has eaten very little of bread-and-meat. Fed 500g. meat.
" 8	7880	A.M. 101^2	290 (with diarrheal feces)		4.9%	All fed eaten. Diarrhea. Not fed today. Very lively.
Abdomen opened by incision in middle line, and without any difficulty or apparent injury to pancreas-remnant, the pancreatic duct was cut between ligatures, omental covering replaced, and abdomen closed. A very short easy operation.						
Jan. 9			No urine.			Very lively. Retains water qs.
" 10			240 (About noon)	1038	1.3%	Lively. Not fed.
" 11	7430		85	1036	Neg.	Fed 200g. horsemeat eaten promptly.
" 12	7200	P.M. 101^8	225	1050	"	Fed 350g. horsemeat and 150g. pancreas.
" 13	7550	A.M. 101	230	1054	3.65%	25g. meat uneaten. Fed 300g. meat and 100g. pancreas: eats pancreas first.
" 14	7600		240	1050	2.4%	All feed eaten. Today fed 350g meat and 150g. pancreas.
" 15	7590	A.M. 101^4	355	1058	3.6%	Fed 400g. beef-heart and 200g. pancreas. Very lively.
" 16	7850	A.M. 100^2	300	1050	3%	All feed eaten. Fed 700g. beef-heart.
" 17	8000		325	1048	1.6%	ditto.
" 18	8200	A.M. 100	270	1058	2.4%	Very strong and lively. Chocolate colored feces, fairly soft and bulky. Today fed 800g. beef-heart.
" 19	8430	A.M. 100^6	200	1060	1.73%	All feed eaten. Fed like yesterday.
" 20	8540	A.M. 101	340	1060	3.3%	ditto.
" 21	8415		466	1058	2.4%	120g. beef-heart uneaten. Fed 700g. beef-heart. Feces always pasty, showing very poor digestion especially of connective tissue.
" 22	8470	A.M. 101^2	240	1064	3.8%	All feed eaten. Very lively. Fed 300g. beef-heart and 300g. pancreas.
" 23	8550	A.M. 100^6	325	1066	4.6%	70g. pancreas uneaten. Fed 300g. beef-heart and 300g. pancreas.
" 24	8500	A.M. 100^4	570	1056	5.2%	All feed eaten. Fed 150g. beef-heart and 150g. pancreas.
" 25	8420	A.M. 100	275	1056	4.8%	All feed eaten. Fed 300g. beef-heart and 300g. pancreas.
" 26	8560		410	1064	7.3%	All feed eaten. Fed 700g. beef-heart.
" 27	8680	A.M. 100^6	410	1060	10.4%	All feed eaten. Fed 700g. horse-meat.
" 28	8750		745	1052	10.4%	100g. meat uneaten. Fed like yesterday.
" 29	8500		640	1053	7.3%	50g. meat uneaten. Fed 700g. beef-heart.
" 30	8525		620	1062	8.1%	50g. beef-heart uneaten. Fed 700g. beef-heart.

DOG 178 (Continued).

Date	Weight g.	Temp.	Urine			Treatment and Remarks.
			Quant. cc.	SpG.	Benedict	
Jan. 31	8285		390	1060	6.4%	225g. beef-heart uneaten. Fed 500g. beef-heart.
Feb. 1	7970		710	1045	8.1%	100g. beef-heart uneaten. Fed 500g. beef-heart. Very lively.
" 2	7895		360	1061	7.3%	60g. beef-heart uneaten. Fed 250g. beef-heart and 250g. pancreas.
" 3	7985		460	1062	12.1%	Feed all eaten. Fed 250g. beef-heart and 250g. pancreas.
" 4	7960		540	1054	12.1%	All feed eaten. Starvation begun.
" 5	7525		240	1048	2.4%	
" 6	7540		(No urine)			
" 7	7360		80	1072	10.4%	
" 8	7210		48	1066	4.8%	
" 9	7180		(No urine)			
" 10	7040		84	1062	7.5%	Starvation continues. At noon, 2g. phloridzin suspended in water given by stomach tube.
" 11	7000		168	1049	6%	Starvation continues. 3g. phloridzin in water given by stomach tube.
" 12	7835		152	1052	6.6%	Starvation continues. 4g. phloridzin in a little water given by stomach-tube.
" 13	7560		180	1051	12.1%	
" 14	6380		50	1068	10.2%	
" 15	6245		28	1088	8.1%	
" 16			52	1065	Slight	
" 17	6265		14	1114	Faint	Given 2g. phloridzin suspended in water by stomach-tube. Is lively and vigorous.
" 18			120	1035	12.1%	Given 3g. phloridzin suspended in water by stomach-tube.
" 19			180	1042	4.5%	
" 20	5740		40	1034	6.8%	
" 21			34	1075	3.8%	
" 22	5600		(No urine)			Becoming dangerously weak therefore fed.
Mar. 2	6400					Lively. Heavy glycosuria.
Apr. 17	4520					
" 23		Dog has grown progressively weaker, and today is unable to stand. Killed by chloroform and autopsied at once. Body greatly emaciated, but traces of fat still discoverable. All the organs, including the liver, are markedly shrunken in size. Liver slightly fatty. Kidneys small; cortex thin. Otherwise negative. Region of pancreas almost free from adhesions. The remnant is atrophied down to the size of a large pea. It is slightly firmer than normal, but the tissue otherwise resembles the normal parenchyma; there is not the marked fibrosis which gross examination often discloses. It has no communication with the intestine. For microscopic findings see Chapter XXI.					

DOG 184.

Male; mongrel, yellowish brown, age two years; medium flesh.

Date	Weight g.	Temp.	Urine			Treatment and Remarks.
			Quant. cc.	Sp.G.	Benedict	
Jan 8	11450					Received. Removal, through incision outside left Rectus, of pancreatic tissue weighing 22.6g. Remnant about main duct estimated at 3g. Ramus pancreaticus inferior ligated, other vessels spared. Omental covering.
" 9						Lively, but vomits.
" 10			250 (first urine since operation)	1052	7.3%	" Retains water qs.
" 11	10750	A.M. 101^4	310	1051	7%	Fed 100g. meat, eaten promptly.
" 12			650	1031	8.1%	Not fed today.
" 13	10090	A.M. 102^6	265	1048	5%	Fed 800g. meat. Slight diarrhea.
" 14	10150	A.M. 102^4	650	1038	6%	200g. meat uneaten. Fed 600g. meat today.
" 15	9790	A.M. 102	555	1053	3%	185g. meat uneaten. Not fed today. Dog is already showing signs of the peculiar diabetic weakness.
Abdomen opened by incision to right of right Rectus. Very few adhesions, except the omentum all in a bunch covering the pancreas remnant. Duodenum was full of food, and its vessels distended with blood. Pancreatic duct was cut between ligatures with minimum of injury of pancreas tissue, and a thick corner of the omental mass was interposed between the divided ends and retained by a suture.						
Dec. 16			755 (before operation)	1014	1.97%	Lively. Retains water qs.
			130 (since operation)	1065	8.1%	
" 17			125	1060	11.2%	
" 18	9220	A.M. 101^2	205	1050	9.1%	Fed 400g. meat. Eats poorly.
" 19			470	1048	10.4%	All feed eaten. Fed 400g. meat. Acts well, but shows very poor appetite.
" 20	8860	A.M. 102^6	840	1040	5.6%	25g. meat uneaten. Fed 300g. meat and 100g. pancreas.
" 21			630	1054	6.8%	All feed eaten. Fed 200g. meat and 400g. pancreas.
" 22	9000	A.M. 102^4	420	1058	12.1%	All feed eaten. Fed 300g. meat and 300g. pancreas.
" 23	9190	A.M. 101^8	415	1054	9.1%	All feed eaten. Fed 400g. meat and 400g. pancreas.
" 24	9100	A.M. 101^8	370	1064	7.3%	140g. pancreas and 160g. meat uneaten. Fed 150g. meat and 150g. pancreas.
" 25	9260	A.M. 101^6	85	1066	7.3%	All feed eaten. Fed 300g. meat and 300g. pancreas.
" 26	9400		665	1052	10.1%	All feed eaten. Fed 600g. meat and 200g. pancreas.
" 27	9590	A.M. 102	745	1050	9%	All feed eaten. Fed 700g. meat and 200g. pancreas.
" 28	9600		885	1046	8.1%	All feed eaten. Fed like yesterday.
" 29	9800		900	1051	8.1%	All feed eaten. Fed 600g. meat and 200g. pancreas.
" 30	9800		220	1066	7.3%	300g. meat uneaten. Fed 400g. meat and 200g. pancreas.
" 31	9715		630	1050	10.4%	All feed eaten. Fed 600g. meat and 300g. pancreas.
Feb 1	9550		530	1062	10.4%	All feed eaten. Starvation begun.
" 2	9265		370	1057	9.1%	
" 3	8980		95	1076	10.4%	
" 4	8750		125	1060	7.3%	
" 5	8595		52	1160	2.4%	
" 6	8465		40	1068	3.3%	
" 7	8285		20	1085	10.4%	
" 8	8220		No urine voided.			
" 9	8050		98	1086	9.1%	
" 10	7925		34	1060	6.6%	
" 11	7870		No urine voided.			
" 12	7630		10	1200	14.6%	
" 13	7460		106	1068	9.1%	
" 14	7300		335	1038	10.4%	

Date	Weight G.	Temp.	Urine			Treatment and Remarks.
			Quant. cc.	SpG.	Benedict	
Feb. 15	7035		360	1082	9.1%	
" 16			70	1072	18.2%	
" 17	6630		122	1065	9.1%	Dangerously weak.
" 18			94	1062	14.6%	Received direct transfusion from a Collie weighing 18,250g. Collie was under ether, this dog under local cocain; and transfusion was continued till blood practically ceased to flow. This dog still staggers from weakness, and no immediate benefit from transfusion is perceptible. Urine lost during operation. No feed given.
Feb. 19			40	1170	9.1%	Shows increased strength. Not fed.
" 20	6350		292	1051	5.6%	Fed 100g. pancreas and 200g. meat.
" 21			510	1050	5.9%	Fed 200g. pancreas and 500g. meat.
" 22	6275		710	1048	6.1%	50g. horsemeat uneaten. Fed 200g. pancreas and 400g. horsemeat.
" 23	6475		825	1050	Heavy	Still dangerously weak, but perhaps gaining. Fed 300g. pancreas and 300g. horsemeat.
" 24	6535		1050	1046	"	ditto.
" 25	6340		500	1055	"	All feed eaten. Same diet. Also, fed 350g. meat and 50g. pancreas extra.
" 26	6565		840	1050	"	All feed eaten. Fed 300g. meat and 300g. pancreas.
" 27			570	1060	"	ditto
" 28			875	1054	"	Not fed today.

(Bladder also full at autopsy)
Dog very weak, therefore killed by chloroform.
Autopsy showed general picture of advanced emaciation.
Thyroid small, normal.
Heart small and flabby.
Lungs normal.
Liver greatly enlarged and very fatty; no adhesions.
Omentum is adherent about pancreas remnant and duodenum, and a number of long bands of adhesions stretch from duodenum to anterior abdominal wall. After stripping the omentum, pancreas remnant appears slightly atrophic, but almost as soft as normal, and with no special degeneration apparent. It does not communicate with bowel. No cysts or other fluid. Weight, free of other tissue, is 4.8g.
Spleen normal.
Kidneys probably normal.
Adrenals are small, with very pale medulla, probably result merely of inanition.
Autopsy otherwise negative.
For microscopic findings see Chapter XXI.

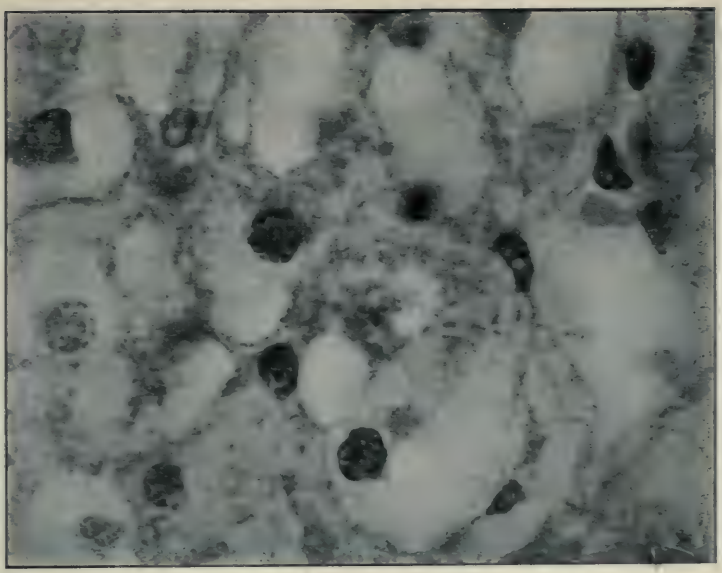


FIG. 1.

Cat 15. (Prolonged dextrose injections.)

Adrenal medulla. Formaldehyde-Zenker; eosin methylene blue. × 1500.

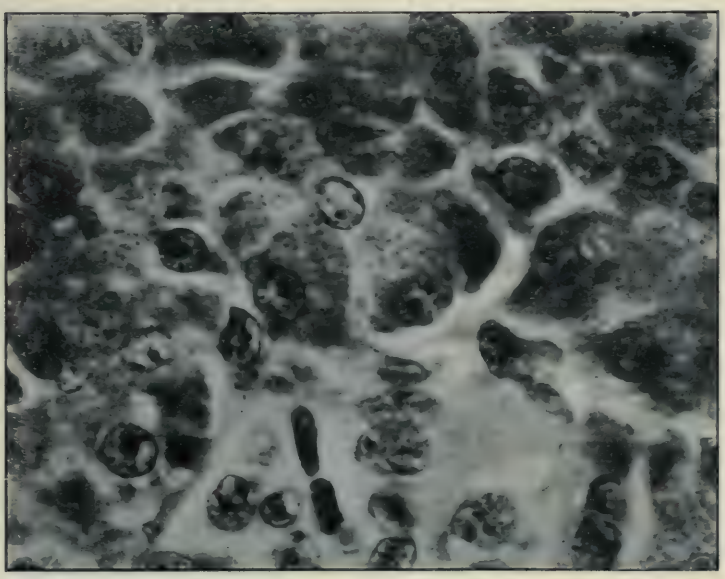


FIG. 2.

Cat 32. (Prolonged starvation.)

Border-zone of islet and acinar tissue. Formaldehyde-Zenker; eosin methylene blue. × 1500.

Though numerous acinar cells, especially in the upper corners of the field, approach the islet form, there is no real transformation or transition.

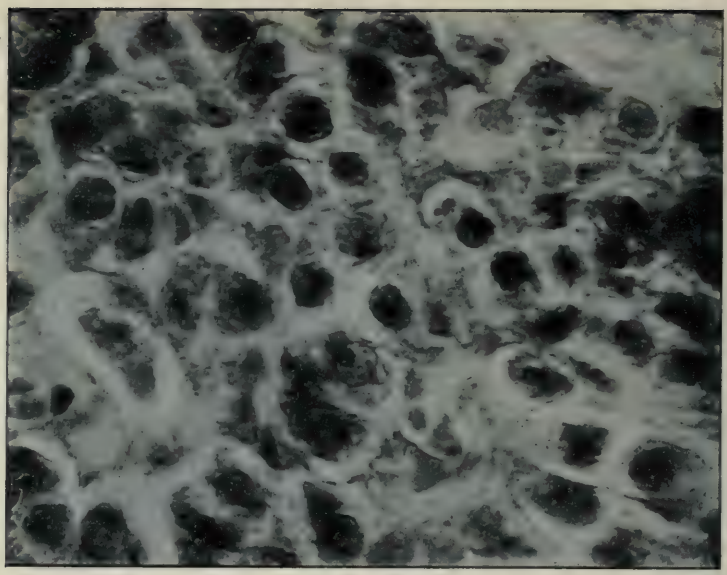


FIG. 3.

Cat 30. (Prolonged starvation.)

Pancreas. Formaldehyde; eosin methylene blue. × 1500. The entire gland consists of small, rounded, poorly differentiated cells, with little or no evidence of acinar arrangement.

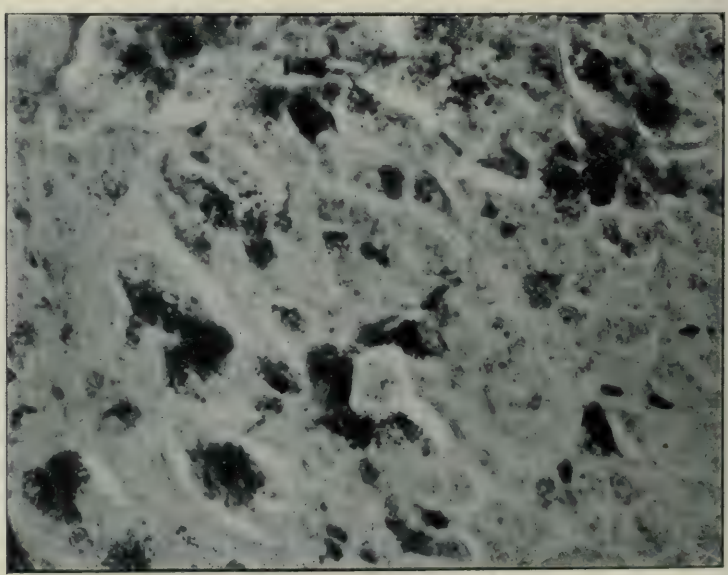


FIG. 4.

Cat 30. (Prolonged starvation.)

Pancreas. Formaldehyde; phosphotungstic acid hæmatoxylin. × 750. The unequal distribution of zymogen granules is shown, and the faint outlines of the numerous small, empty cells. Focussing under high power shows every granule in the dark masses to be of shot-like distinctness.

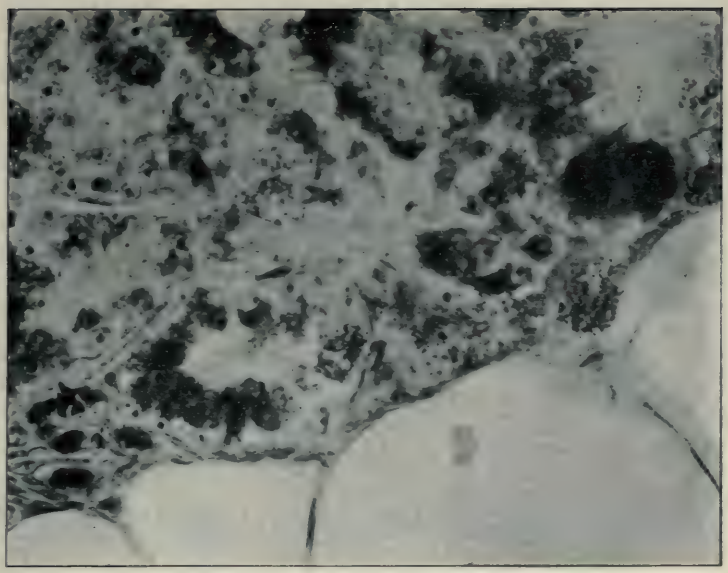


FIG. 5.
Dog 21.
Pancreas. Formaldehyde; phosphotungstic acid hæmatoxylin. × 750. Border-line of pancreas-tissue and lipoma. Unequal distribution of secretion granules.

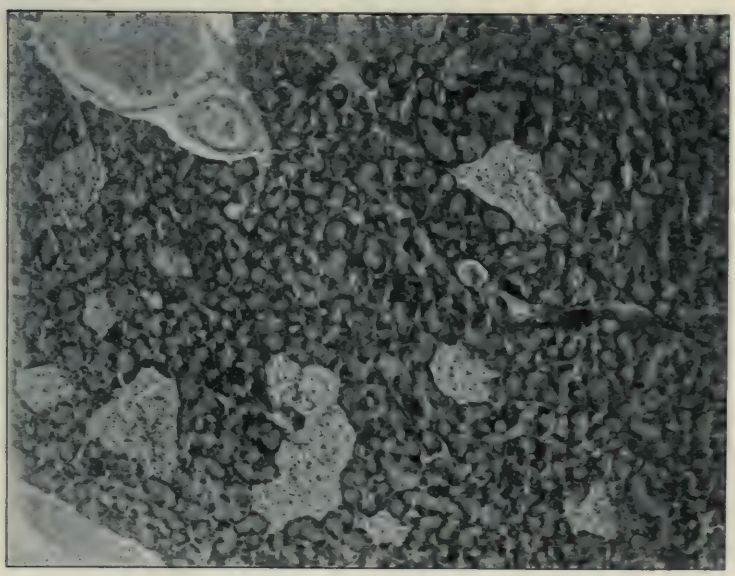


FIG. 6.
Dog 73. (Obliteration of portal vein. Diabetes insipidus.)
Pancreas. Formaldehyde; eosin methylene blue. × 133. Hyperemia. Unusually numerous and prominent islets full of normal cells.

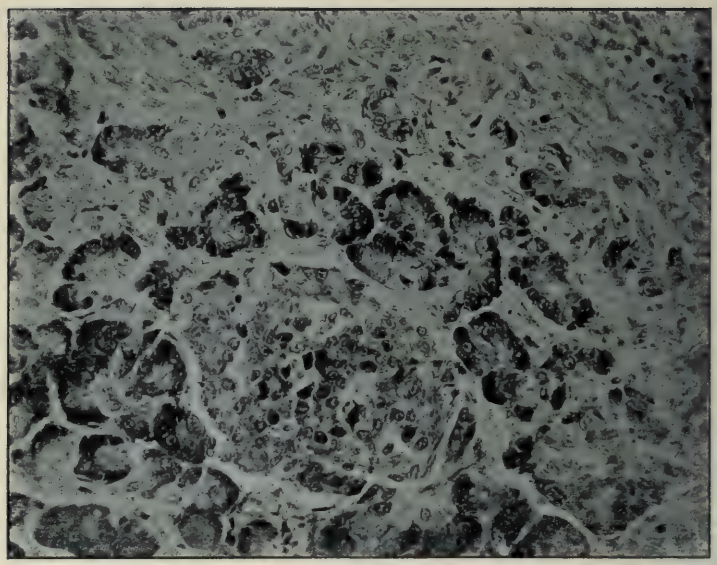


FIG. 7.

Dog 173. (Partial pancreatectomy. Ligation of duct. Diabetes absent.)
Pancreas. Zenker; eosin methylene blue. × 310. Border-line of pancreas-remnant and enveloping scar-tissue. Well preserved islet.

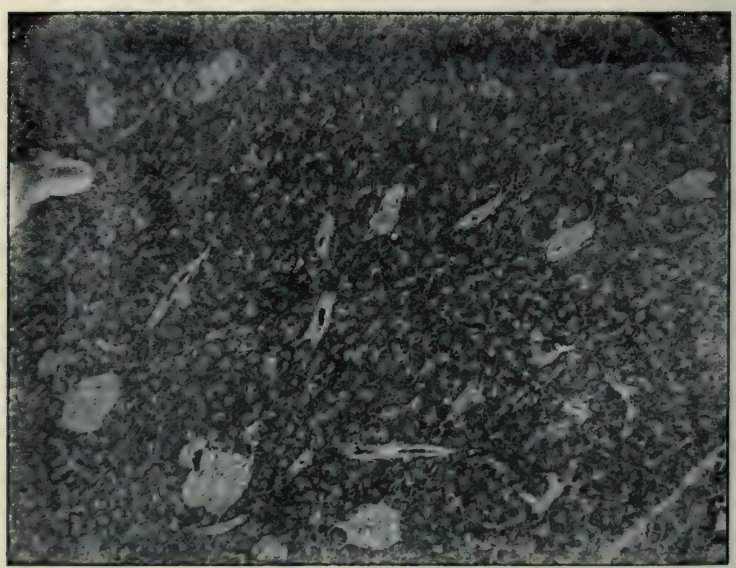


FIG. 8.

Dog 185. (Transient diabetes gravis.)
Pancreas. Zenker; eosin methylene blue. × 100. Unusual number of small ducts, recognizable by the stained secretion in them. Numerous islets, mostly small and elongated, apparently developing from ducts.

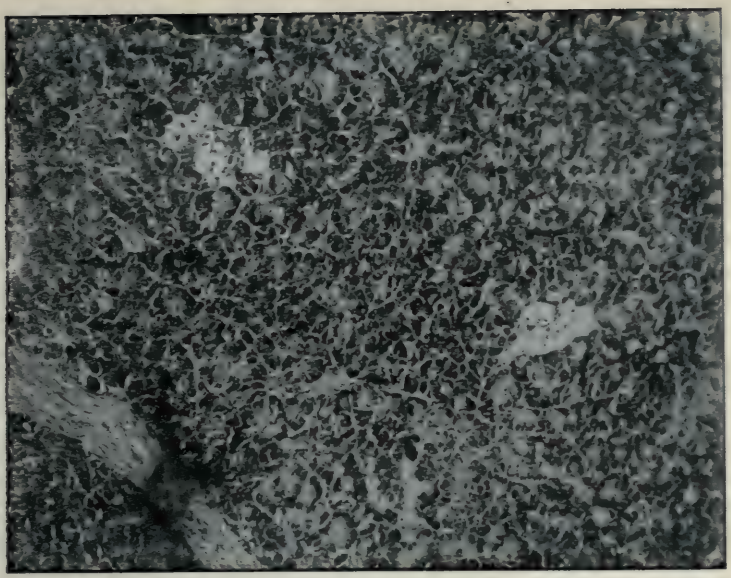


FIG. 9.

Dog 38. (Diabetes.)

Pancreas. Formaldehyde; eosin methylene blue. × 150. Normal acinar tissue. Two islets, showing the typical degeneration as seen under low power.

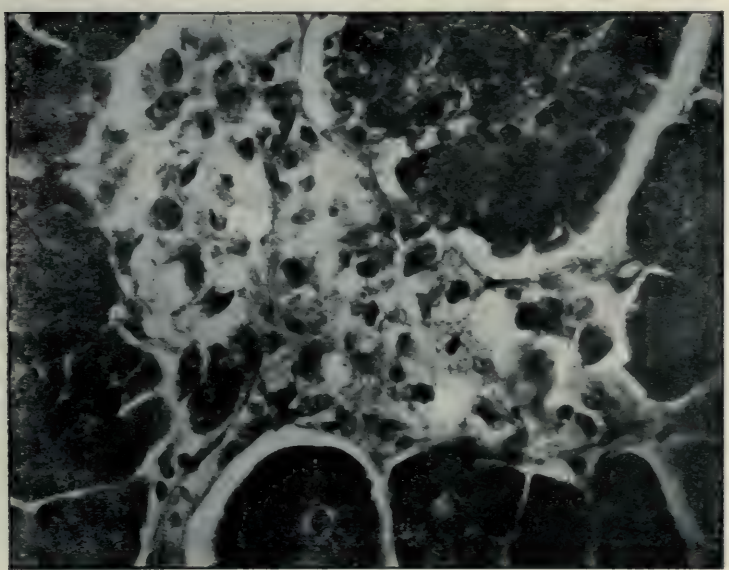


FIG. 10.

Dog 63. (Partial pancreatectomy. Piqûre. Diabetes.)

Pancreas. Formaldehyde; eosin methylene blue. × 620. Degeneration of islet.

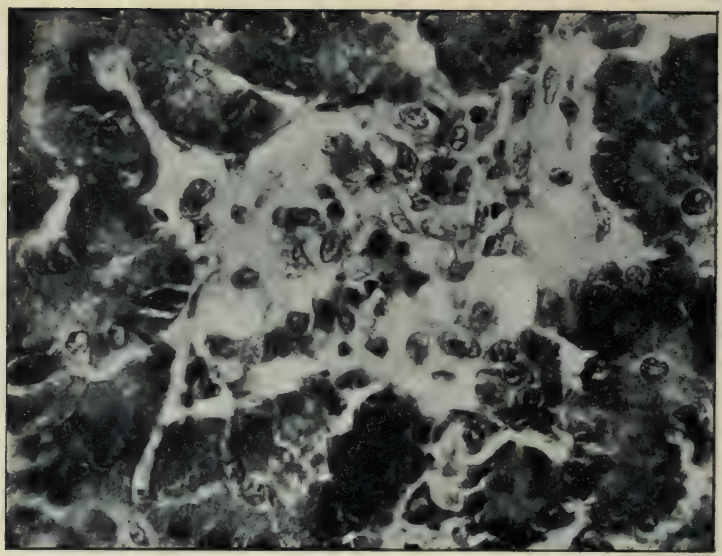


FIG. 11.
Dog 146. (Diabetes.)
Pancreas. Formaldehyde; eosin methylene blue. × 750. Degeneration of islet.

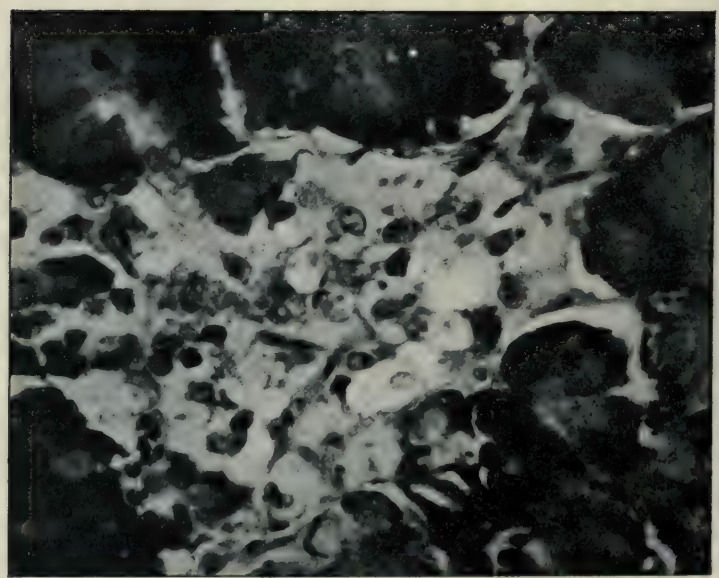


FIG. 12.
Dog 154. (Diabetes.)
Pancreas. Formaldehyde; eosin methylene blue. × 620. Degeneration of islet.

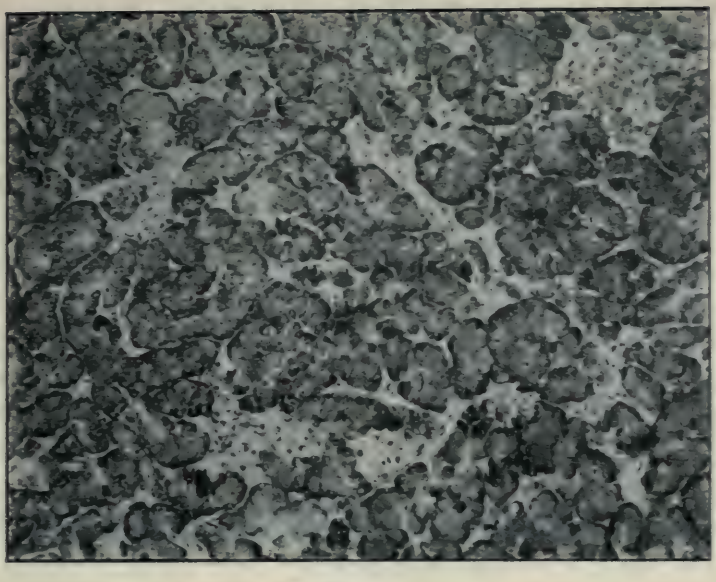


FIG. 13.

Dog 167. (Obliteration of portal vein. Diabetes.)

Pancreas. Zenker; eosin methylene blue. × 300. Degeneration of islets, less advanced than in the preceding animals. The islet in the right upper corner is changed less than that towards the left lower corner. The usual sprinkling of pyknotic nuclei.

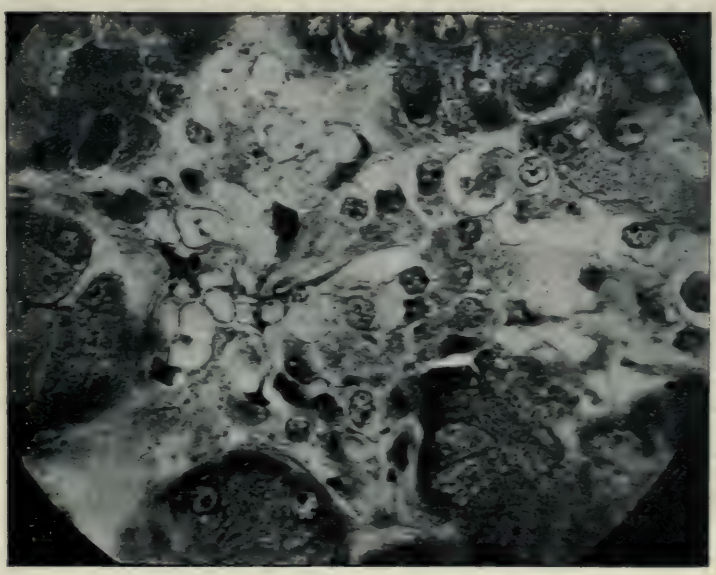


FIG. 14.

Dog 167. (A field from the same section as Fig. 13.) × 750. Degeneration of islet.

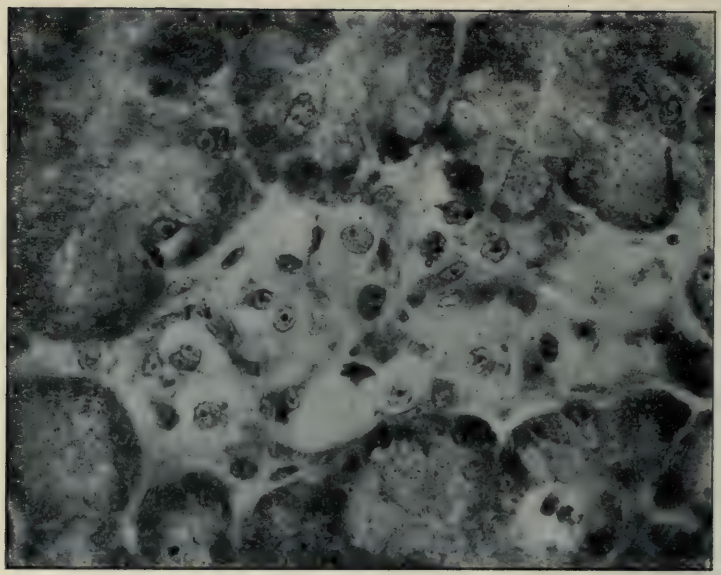


FIG. 15.
Dog 178. (Diabetes. Subsequent duct-ligation.)
Pancreas. Zenker; eosin methylene blue. × 750. Good preservation of acinar tissue.
Moderate degeneration of islet.

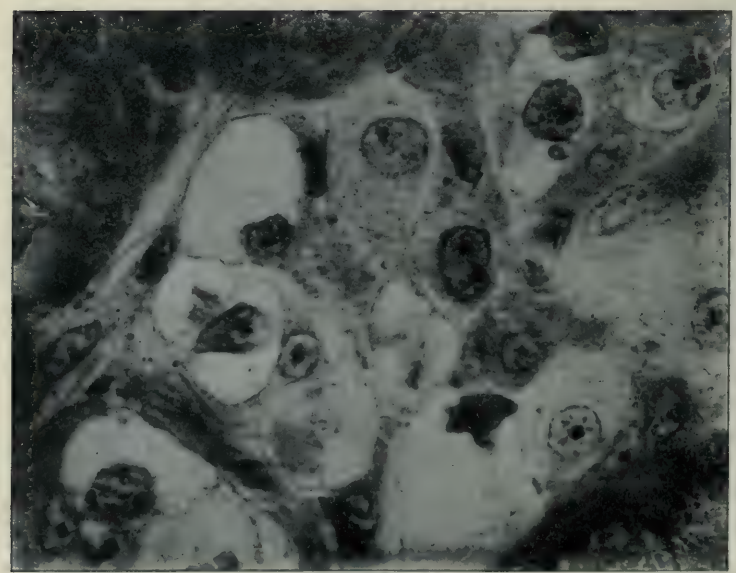


FIG. 16.
Dog 178. (A field from the above section.) × 1500.
Detail study of earlier stages of degeneration of islet.

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